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**University Clinic of Psychiatry  
41 Nicolae Romanescu St., 200317 Craiova, ROMANIA  
Tel: +40 251 426020; Fax: +40 251 428584  
E-mail: [editor@psychopharma.eu](mailto:editor@psychopharma.eu)  
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**On the Cover:**

**ION ȚUCULESCU (1910-1962)**

**Căldură**  
*Warmth*

## PHARMACOLOGIC TREATMENT IN OLD-AGE MAJOR DEPRESSION: A SYSTEMATIC LITERATURE REVIEW

Octavian Vasiliu<sup>1\*</sup>, Victor Voicu<sup>2</sup>, Daniel Vasile<sup>1,3</sup>

<sup>1</sup>University Emergency Military Central Hospital “Dr. Carol Davila”, Bucharest, Romania

<sup>2</sup>Romanian Academy, Bucharest, Romania

<sup>3</sup>University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania

### **Abstract**

*Old age major depression presents some real clinical and therapeutic challenges for psychiatrists, due to peculiarities of this pathology during the third phase of life. A systematic literature review was considered necessary in order to find out if clear, evidence-based recommendations could be formulated in this domain. Main medical databases - PUBMED, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Complete MEDLINE, National Library of Medicine and the National Institute of Health (NCBI), PsycINFO and Cochrane Collaboration- were searched for clinical trials, systematic reviews and meta-analyses focused on antidepressants used for treatment of old age population with major depression. Data analysis sustained the recommendation for SSRIs (except for fluvoxamine), venlafaxine, mirtazapine and nortriptyline in this population. Minimum duration for confirmation of the therapeutic response to an antidepressant, based on data analysis, is 6 weeks. Response rate fluctuates according to sex, age, medium duration of the current episode, initial severity of depression, number of depressive episodes.*

**Keywords:** major depressive disorder, antidepressants, old-age population, response rate.

### **Background**

Antidepressants stand as the first line of major depression treatment in patients of all ages, but their efficacy and tolerability have specific features depending on physiologic and pharmacologic characteristics of the target population, like metabolism rate, elimination rate and distribution volume. Other important factors mediating therapeutic response and tolerability in old-age patients are interactions of antidepressants with other concomitant drugs (frequently used in these patients), combinations of treatment side events and somatic symptoms deriving from comorbidities, impact of the cognitive decline over therapeutic adherence, specific sensitivity to some pharmacodynamic properties of the drugs (i.e. tricyclics induced anticholinergic adverse events may aggravate neurocognitive performances).

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\* Correspondence: Octavian Vasiliu, University Emergency Central Military Hospital “Dr. Carol Davila” Psychiatry Department, M. Vulcanescu Str, no. 88, Bucharest, Romania. E-mail: octavvasiliu@yahoo.com.

Although old age depression is associated with severe impact over the patients' performances in daily activities, significant caregiver burden and healthcare services burden, only a minority of these patients receive adequate antidepressant treatment in primary or secondary care. It was estimated that only about 10-20% of all depressed elderly patients receive correctly prescribed antidepressant treatment [1,2].

Antidepressants, as a pharmacologic class, decrease suicide risk in patients aged over 65, compared to placebo, according to data from retrospective analyses [3]. Therefore, old age patients diagnosed with depression who receive antidepressants may have a reduced risk for suicide attempts. Even if SSRIs could increase impulsive acts, these drugs decrease overall risk for suicide, especially in elderly males, and a high rate of antidepressant prescriptions may diminish self-aggressive risk, even in hospitalized patients [4].

## **Objectives**

This literature review has as main objectives detecting differences between antidepressants in efficacy and tolerability in old age patients diagnosed with major depressive disorder.

## **Methods**

A database search using specific keywords according to the above mentioned objectives was the selected method for extracting relevant data in order to formulate treatment recommendations.

Searched databases were PUBMED, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Complete MEDLINE, National Library of Medicine and the National Institute of Health (NCBI), PsycINFO, and Cochrane Collaboration. We included randomized trials published in English, between 1980 and 2015. Also, we included a separate analysis of other systematic literature reviews and meta-analyses which corresponded to this review's objectives.

Keywords used for search were „old age depression”, „late life depression”, combined with „antidepressants”, „antidepressants and psychotherapy”, and also international nonproprietary names (INN) of all marketed antidepressants listed in section 5 of this paper. We excluded trials based only on psychotherapy or other, non-pharmacologic interventions.

## **Population characteristics**

There is some degree of controversy in the literature regarding the definition of „old age” population, which is an obstacle for a clear delineation of „old age depression” group. According to developmental psychology perspective, Erik Erikson states as cut-offs 20-30 years old (young adults), 30-65 (mature adult) and over 65 years old (old age adult) [5]. Erikson bases his cut-off for old age adult on phase-specific processes, like the decrease of physical abilities, retirement and lower income, establishment of relationships with other age group individuals, and facing spouse death.

Another perspective is Neugarten's, who differentiates between people aged 55 to 75 („young-old”) and those over 75 („old-old”), suggesting that age-related negative social stereotypes (e.g. being sick, alone, without libido, moving more slowly etc) are based on observation of the very old people [6]. Due to this fact, there are difficulties in the correct perception of those who have an intermediate age, between adult and old-age.

On the other hand, UN suggests for the statistical processing of epidemiologic data a cut-off of 60 for elderly population, stating that this will overcome differences between developed countries and less developed ones, since the latter have a lower life expectancy [7].

Although arguments stated by developmental psychology are sufficiently sound to establish a cut-off of 65 as limit for elderly population, we used the UN cut-off of 60 because the life expectancy differences between societies is considered an important issue that could limit the generalization of collected data.

<b>OPERATIONAL CRITERIA</b>	<b>INCLUSION CRITERIA</b>	<b>EXCLUSION CRITERIA</b>
<b>POPULATION</b>	Patients aged over 60, diagnosed with major depressive disorder, either first episode or recurrent, according to the DSM/ICD criteria, or compatible with these two classifications, who don't have other significant psychiatric comorbidities, except for neurocognitive disorders (only moderate/mild stages)	Young and adult population, defined by a maximum age of 59. Psychiatric comorbidities, severe forms of neurocognitive disorders, drug related or induced disorders, severe anxiety disorders. Severe organic diseases which interfere with cognitive abilities (e.g. thyroid diseases, vitamin deficiencies, brain tumors) Bipolar depressive episodes were excluded whenever the trial inclusion/exclusion criteria were enough explicitly formulated to allow such a differentiation.
<b>INTERVENTION</b>	Any type of antidepressant. Combination of antidepressant and structured psychotherapy	Unstructured or insufficiently detailed psychotherapy setting, especially when used as the single intervention. Other treatment interventions, like electroconvulsive therapy, light-therapy, transcranial magnetic stimulation etc. Use of OTCs as monotherapy and use of any product without a proven antidepressant effect, including investigational products (phase I to III)
<b>SETTINGS</b>	In-patients or out-patients. Caregiver is involved or not. Institutionalized or independent community dwelling patients.	Unspecified settings, carceral institution
<b>PRIMARY AND SECONDARY OUTCOMES</b>	Depressive symptoms severity decrease, based on psychometric measurements. Tolerability of antidepressants.	Trials which didn't specify psychometric instruments used, trials which used insufficiently validated scales and trials which used only global functioning scales as measurements
<b>STUDY DESIGN</b>	Randomized clinical trials (RCTs), controlled clinical trials Other systematic analyses and meta-analyses were included in a separate review, then compared to the primary review	Trials with no specified design, retrospective trials, observational trials.
<b>LANGUAGE</b>	English	Any other languages except for English

## Types of intervention

We selected for this review trials with antidepressants, and we excluded food supplements, OTCs, other products without insufficiently established efficacy (e.g. S-adenosylmethionine, omega-3 fatty acids), antipsychotics used as monotherapy (e.g. quetiapine, olanzapine), mood-stabilizers as monotherapy (e.g. lamotrigine), and investigational products.

Antidepressants used as keywords for the database search are:

- tricyclics and tetracyclics (amitriptyline, clomipramine, imipramine, doxepin, dosulepin/dothiepin, desipramine, lofepramine, nortriptyline, protriptyline, trimipramine, mianserin, maprotiline);
- serotonin selective reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline);
- serotonin and norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran);
- monoamine oxidase inhibitors (isocarboxazide, tranylcypromine, phenelzine), reversible inhibitors of monoamine oxidase A (moclobemide);
- noradrenergic and specific serotonergic agents (mirtazapine);
- melatonergic agonists and 5HT<sub>2</sub> receptors antagonists (agomelatine);
- glutamatergic modulators (tianeptine);
- selective noradrenaline reuptake inhibitors (reboxetine, atomoxetine);
- dopamine and noradrenaline reuptake inhibitors (bupropion);
- 5HT<sub>2</sub> antagonists and serotonin reuptake inhibitors (trazodone, nefazone).

Clinical trials with combinations of antidepressants or augmenting agents added to standard antidepressants were included, target population could have any severity of depression and any type of response (complete=remission/partial=response/absent) to antidepressant treatment.

Patients received antidepressant treatment in institutionalized regimen, during hospitalization, or during an out-patient regimen.

Combined regimens of antidepressants and structured psychotherapy were allowed.

## Outcomes and comparison of primary variables

Clinical trials included in this review were described according to the following categories:

- international non-proprietary name (INN) of the antidepressant drug, dosage regimens;
- authors of the published paper;
- study objective(s);
- study design;
- population characteristics, especially minimum age for admission in the trial;

- primary and secondary outcomes;
- results.

Outcome analysis depended on studies design, based on comparison of efficacy between two or more interventions in parallel groups, comparison of efficacy between an active agent and placebo, or monitoring the action of a single agent without an active/inactive comparator. Prospective, as well as retrospective studies were included.

Limitations of this analysis are related to variations of group characteristics, which make difficult to eliminate some variables influence over final results (e.g. number of previous depressive episodes, type of previous treatments etc). Duration of the treatment administration varied between trials, control groups were not valid in each case, and group sizes varied significantly, in some cases being too small for a powerful statistical analysis.

Changes in the severity of depression using standardized clinical scales and tolerability of the antidepressant drugs were primary outcomes.

## Results

This systematic review is based on randomized clinical trials and its results have been compared with other reviews and meta-analyses, in order to avoid the over-inclusion of several trials in both types of comparisons.

Level of trials significance has been established using the following categories: 5- prospective clinical trials, randomized, double blind, placebo controlled; 4- prospective clinical trials, randomized, single blind; 3- open label trials; 2- retrospective trials; 1- other types of clinical trials. A number of 23 clinical trials were selected according to the inclusion and exclusion criteria, with a 3 to 5 level of significance.

Therapeutic action of **venlafaxine** has been studied in a trial which detected several factors associated with a lower probability to induce remission (e.g. higher initial severity of symptoms, smaller improvement during the first two weeks of treatment, or being male) [8]. The same trial showed that a decrease of HAMD scores with over 27% and MADRS initial scores of 27 are associated with highest rate of symptoms remission. Also, age of 60-75 is associated with higher rate of remission compared to 75+ [8].

**Venlafaxine** and **nortriptyline** has been associated with similar results, and no difference was detected regarding tolerability in old age population with major depression [9,10].

Antidepressant should be changed if elderly patients didn't respond after 3 to 4 weeks (under 30% improvement on depression scales) [10].

**Venlafaxine or nortriptyline treatment augmentation with lithium** is an efficient option in elderly population, compared to MAOIs and ECT [11]. **Augmentation of antidepressant**

**treatment with lithium** versus placebo+antidepressant lead to a reduced rate of relapse and was well tolerated in a 2 years trial [12].

**Duloxetine** improves anxiety and pain symptoms in patients aged over 65 with major depressive disorder [13].

**Paroxetine** and **paroxetine CR** improved anxiety and depressive symptoms in patients with affective disorders, and the response was better in those with a gradually increased dose [14, 15].

**Paroxetine and interpersonal therapy** showed a significant improvement of life quality, within all its domains, except for physical activity, both during acute phase, and maintenance phase [16]. The same paroxetine and interpersonal therapy combination has been associated with a superior efficacy in preventing depressive recurrences versus paroxetine and clinical management, placebo and interpersonal therapy, and placebo plus clinical management [17]. Rate of recurrence in depressive disorder was 2.4 times greater in those receiving placebo, comparative to those treated with paroxetine [17]. **Paroxetine** has been associated with negative results in very old, institutionalized patients diagnosed with major depression, being associated with a similar efficacy with placebo and a higher rate of cognitive side effects (as reflected by MMSE score decrease) [18]. Still, this trial included a small number of subjects (n=24) and they were institutionalized, so various factors altering treatment response could be taken into consideration (like social negative inferences, physical circumstances etc.)

**Citalopram** has been evaluated in a negative prognosis factors detection trial in elderly patients with depressive disorder and concluded that response inhibition, a basic executive function, predicts a poor response to antidepressants [19]. Citalopram induced a remission rate of 35%, and those with a more severe at the admission had a higher rate of remission under pharmacologic treatment comparative to placebo [20]. **Citalopram and mianserin** induced higher decreases of depression scores in patients that presented only depression versus those with depression and dementia, with a good tolerability [21].

**Fluoxetine** determined a higher improvement than in patients with placebo on all monitored scales, SF-36 included [22].

**Tricyclic antidepressants plus interpersonal therapy** lead to a 78.4% remission rate in old age patients (using nortriptyline) and 69.6% rate in adults (using imipramine), and a relapse rate of 15.5% in elderly comparative to 6.7% in adults [23]. This trial concluded that old age patients benefit from antidepressant treatment similar to adults, but therapeutic response may have a slower onset, and relapses may be more frequent in elderly [23].

**Clomipramine** was evaluated in old age female and the results were positive [24]. **Dothiepine** decreases relative risk of relapse by 2.5 times, and a prolonged depressive episode necessitates minimum 2 years duration of therapy, or the therapy may be continuous [25].

**Sertraline** and **mirtazapine** are efficient comparative to placebo after 13 weeks, differences between them being small ( $p=0.112$ ) [26]. Mirtazapine orodispersible tablets administered in institutionalized patients aged 85+ provoked a decrease of depression severity on the evaluation scales with over 50% after 12 weeks, while the CGI score increase over 55% [27].

Switching on **phenelzine** has been compared with lithium augmentation in patients who didn't respond to tricyclics or venlafaxine, and results showed a superior efficacy for lithium [28].

**Venlafaxine** is the most studied drug from the SNRI category in the elderly, and its evaluation has been made during several clinical trials with a moderate level of significance ( $n=4$ , medium score 3.75). Another SNRI agent, duloxetine, proved a high efficacy on anxiety and pain symptoms associated to geriatric depression.

If the results are clustered according to the antidepressant classes, we have the following situation:

From the SSRI class, **paroxetine** was the most studied drug and it was associated with positive results, both in monotherapy and in association with interpersonal therapy ( $n=4$ , medium score 4.5), but there are also negative reports ( $n=1$ , level of significance=5). Efficacy of paroxetine +/- interpersonal therapy was high, both on short-term and on long-term, significantly decreasing recurrence risk versus placebo.

**Citalopram** has been evaluated in 3 studies with a maximum level of significance and induced positive results. **Fluoxetine** was evaluated in only one study with high level of significance and its efficacy was good. **Sertraline** was associated with favorable results, comparative with mirtazapine, while tolerability was similar in both cases ( $n=1$ , level of significance =5).

From the **tricyclics** class a number of agents were evaluated- nortriptyline, imipramine, clomipramine, dothiepine (dosulepin) ( $n=6$ , medium score =3.83)- and determined favorable results, but with a slower onset and a higher rate of relapses in old age population. **Nortriptyline** is the best studied drug from this class and it was also well tolerated in this population.

**MAOIs** were identified in two trials, with a medium level of significance of 3.5. Phenelzine is inferior to the lithium+antidepressant agent combination in patients who previously presented an insufficient response to an antidepressant.

**Mirtazapine** had efficacy and tolerability similar to sertraline ( $n=2$ , medium score =4).

**Table 1.** Clinical trials focused on old age depression treatment

Intervention	Authors	Objectives	Design	Population	Out comes	Results	LS
Venlafaxine SR up to 300 mg daily	Joel I, Begley AE, Mulsant BH et al. [4]	Identification of remission predictors in major depression	Venlafaxine (37.5-300 mg/day) open label, 12 weeks, N=277	≥60 years old	MADRS, HDRS-17, SSI, PSWQ, BSI	Initial severity of depressive symptoms, less improvement during first 2 weeks of treatment ( $p<0.001$ ), being male ( $p=0.03$ ), minimum 2 years of depressive symptoms ( $p<0.001$ ), previous adequate treatment ( $p=0.06$ ) predict a lower rate of remission; MADRS decrease with >27% and initial MADRS score <27 are associated with the highest rate of symptoms remission (89%); Age <75 is associated with the lowest rate of remission (16%)	3
Paroxetine 10 mg (complete initial dose vs. gradually dose increase)	Gibiino S, Mori E, De Ronchi D, Serretti A. [14]	Titration Regimen comparison in old-age patients - sudden vs. gradually	Observational 8 weeks, N=50	≥60 years old	HAMD-21, domains from HAMD (psychic anxiety, somatic, core symptoms)	Amelioration of anxiety and depressive symptoms is significantly higher in those with a gradually dose increase (HAMD $p=0.014$ , HAMA $p<0.001$ ); higher rate of discontinuation if doses are not gradually increased	3

Intervention	Authors	Objectives	Design	Population	Outcomes	Results	LS
Sertraline, mirtazapine	Banerjee S, Hellier J, Romeo R et al. [26]	Efficacy of sertraline and mirtazapine, target doses 150 mg and 45 mg respectively, 13 weeks, N=326	Multi-centric, parallel groups, double blind, placebo controlled, randomized	Not specified (senior), comorbid mild or moderate dementia	CSDD, CSRI	Difference on CSDD after 13 weeks between sertraline and placebo (p=0.102), placebo-mirtazapine (p=0.991), mirtazapine-sertraline (p=0.112); those who received placebo had less adverse events (26%) than those who received sertraline (43%) or mirtazapine (41%)	5
Donepezil+anti depressant vs. antidepressant+ placebo	Reynolds CF 3rd, Butters MA, Lopez O et al. [29]	Donepezil plus antidepressant and antidepressant therapy are superior to placebo+antidepressant on cognitive function and daily instrumental activities, as well as in reducing depressive recurrences during 2 years of treatment	Randomized, double-blind, placebo controlled, N=130	≥65 years old	17 neuropsychologic tests, IADL, HAMD17	Donepezil+antidepressant improve cognitive function, but the effect was considered of medium size after one year; moderate effect on cognitive daily instrumental activities (p=0.6); those who received donepezil had higher risk than placebo for recurrent major depression; donepezil has no efficacy in preventing depressive recurrences in patients without cognitive impairments	5
Venlafaxine vs. nortriptyline	Kok RM, Aartsen M, Nolen WA, Heeren TJ [9]	Tolerability of antidepressants in elderly patients with major depressive disorder	Double-blind, randomized, then open label phase, 3 years, N=43	Not specified (old age)	SSSEC, MADRS	No difference regarding tolerability and efficacy between the two agents; adverse events decreased gradually; there is an association between depression severity and adverse events severity, but the connection between antidepressant dose and adverse events severity was only marginal significant	5
Venlafaxine vs. nortriptyline	Kok RM, van Baarsen C, Nolen WA, Heeren TJ [10]	Predictors of depression remission in elderly patients with major depression	Randomized, controlled, N=81, 12 weeks	Not specified (old-age)	HAMD, MADRS	Antidepressant treatment must be changed if old age patients have a smaller than 30% response after 3-4 weeks on depression scales	4
Venlafaxine/nortriptyline+lithium, MAOIs or ECT	Kok RM, Nolen WA, Heeren TJ [11]	Pharmacologic sequential treatment evolution in old-age patients with severe depression	Open label, sequential, 3 years, N=32	Not specified (old-age)	MADRS	Remission rate (maximum MADRS score of 10) 84%, response rate (over 50% reduction of MADRS score) 96.3%, higher severity and longer duration of the initial depressive episode predict a smaller response; lithium augmentation may be the best option in elderly patients with major depression	3
Paroxetine, paroxetine	Rapaport MH, Lydiard RB, Pitts CD et al. [15]	Efficacy and tolerability of paroxetine CR small daily doses	Multicentric, placebo controlled, double-blind, fixed dose, randomized, N=525, 10 weeks	Not specified (old age)	HAMD, CGI	-1.8 (p=0.029) paroxetine CR 12.5 mg, -3.3 (p<0.001) paroxetine CR 25 mg; remission (maximum HAMD score 7) reached more frequently by those receiving paroxetine CR 25 mg (41%, p=0.008); CGI-S improvement for both paroxetine CR doses vs. placebo; better tolerability for both paroxetine CR, similar to placebo. Quality of life was improved (p<0.001) by both doses of paroxetine	5
Phenelzine, augmentation with lithium of the previous antidepressant therapy	Kok RM, Vink D, Heeren TJ, Nolen WA [28]	Phenelzine efficacy in patients who didn't respond to tricyclics or venlafaxine	Hospitalized patients, open label, randomized, controlled 2 years follow-up, N=29	Not specified (old-age)	MADRS, HAMD (primary target was remission, defined by MADRS score of maximum 10; the response is defined by minimum 50% decrease in MADRS/HAMD scores)	Remission rate 33.3% (lithium), 0 (phenelzine) (p=0.042). Response was in favor of lithium augmentation (p=0.035 on MADRS, HAMD). Overall tolerability was good. At the 2-years follow-up, 86.2% reached remission, especially those with prolonged lithium treatment or those with phenelzine+lithium.	4
Paroxetine plus IPT	Dombrovsky AY, Lenze EJ, Dew MA et al. [16]	Quality of life in patients with major depression who didn't respond to a short duration treatment	Double-blind, placebo controlled, paroxetine vs. placebo, monthly IPT vs. clinical management, one year, N=195	≥70 years old	QWB, 6 specific domains of the HR-QOL	All domains of HR-QOL, except for physical functioning, improved significantly during acute phase, but also during the continuation phase; pharmacotherapy was superior to placebo after the control of psychotherapy effects in domains like general well-being, social functioning, limitation of roles due to emotional problems	5
Citalopram 20-40 mg/day	Sneed JR, Roose SP, Keilp JG et al. [19]	Negative prognosis factors during antidepressant treatment	Double blind, placebo controlled, 8 weeks	≥75 years old	SCWT for executive dysfunction	Response inhibition, a fundamental executive function, predicts a low response rate to antidepressant treatment	5
Mirtazapine orodispersible tablet	Nelson C, Hollander SB, Betzel J et al. [27]	Efficacy of orodispersible mirtazapine in institutionalized elderly patients	Multicentric, open label, 12 weeks, N=50	≥85 years old, mean age 89.3	HAMD-16, CGI, CSDD, MMSE ≥10 at inclusion	HAMD score decreased from 16.9 to 7.3; CSDD score decreased from 15.1 to 7.1; CGI-I improved with 55%; 10% discontinuation related to adverse events.	3
Paroxetine plus IPT	Reynolds CF 3rd, Dew MA, Pollock BG et al. [17]	Efficacy of paroxetine in elderly patients with depression, either first episode, or recurrence	Double blind, placebo controlled, 2x2 model (IPT+ paroxetine, IPT+ placebo, paroxetine+ clinical management, placebo+clinical management), 2 years, N=116	≥70 years old	Relapse prevention is the primary target. Secondary targets are MMSE, MATTIS-DRS, QWB, HAMD, SHQ	Recurrences 35% for paroxetine+IPT, 37% for paroxetine+ clinical management, 68% for placebo+IPT, 58% for placebo+clinical management (p=0.02); after the IPT effect adjustment, recurrence RR in patients receiving placebo was 2.4 times higher than in those receiving paroxetine	5
Citalopram 10-40 mg/day	Roose SP, Sackeim HA, Krishnan KR, et al. [20]	Efficacy of citalopram	Multicentric, randomized, placebo controlled, institutionalized patients, N=174	≥75 years old, mean age 79.6	HDRS	Remissions (defined by a HDRS score of max 10) 35% for citalopram, 33% for placebo; patients with initial more severe depression (HDRS >24) had a higher rate of remission with medication (35% vs. 19%)	5
Sertraline (≤100 mg/day), venlafaxine (≤150 mg/day)	Oslin DW, Ten Have TR, Streim JE et al. [21]	Safety of antidepressant medication in institutionalized old age patients	Double-blind, randomized, controlled, venlafaxine vs. sertraline, 10 weeks, N=52	Not specified (old age)	HAMD, number of adverse events, time to discontinuation (SAE, AE, informed consent withdrawal)	Mean HAMD scores decreased similarly in both groups (from 20.2 to 12.2 for sertraline, 20.3 to 15.7 for venlafaxine, p=0.069); estimated tolerability based on time to discontinuation for any reason was smaller for venlafaxine	5
Paroxetine	Burrows AB, Salzman C, Satlin A et al. [18]	Efficacy of paroxetine in institutionalized, very old patients	Double blind, placebo controlled, 8 weeks, institutionalized non-major depression, N=24	Mean age 87.9	CGI-I, HDRS, CSDD, MMSE	Efficacy of paroxetine is not clearly superior to placebo, there is a risk for cognitive side effects; paroxetine was associated with a higher risk for delirium and decrease of the MMSE score	5
Citalopram (20-40 mg/day), mianserin (30-60 mg/day)	Karlsson Godderis J, Augusto de Mendoca Lima C et al. [30]	Citalopram and mianserin efficacy and tolerability	Randomized, double-blind, N=336, major depression +/- mild/moderate dementia, 12 weeks	Not specified (old age)	MADRS	Patients diagnosed with dementia had a smaller decrease of the MADRS scores, comparative to those who had only depression; both antidepressants had good tolerability- fatigability and drowsiness more frequently reported by mianserin treated subjects, insomnia reported more frequently by citalopram treated patients	5

Intervention	Authors	Objectives	Design	Population	Outcomes	Results	LS
Lithium augmentation of the antidepressant therapy	Hardy BG, Shulman KI, Zucchero C. [12]	Lithium tolerability	Lithium vs. placebo during continuation phase, N=12, 2 years	Not specified (old age)	MADRS, GDS, composite score with 21 items regarding adverse events	2 cases of recurrence in lithium treated patients, after 61 and 96 weeks, related to stressful life events; 2 recurrences in placebo group at 7 and 92 weeks, with no obvious provoking event; depression was observed in those receiving placebo and was relatively resistant to reinitiation of lithium as augmentation agent	4
Tricyclic antidepressant (nortriptyline for elderly and imipramine for adults)+IPT	Reynolds CF 3rd, Frank E, Kupfer DJ et al. [23]	Response rates, symptoms evolution during acute treatment, relapse rates during treatment discontinuation phase in elderly subjects and old age and adults with recurrent major depression	Two controlled trials, open label, acute phase and therapy continuation, N=148 elderly subjects and N=214 adults	Elderly (mean age 67.9) and adults (mean age 38.5)	HAMD	Remissions: 78.4% elderly and 69.6% adults. Adults had a faster decline of the HAMD scores. After stabilization, 15.5% of the old age patients and 6.7% of the adults relapsed. 66.2% of the elderly and 50.7% of the adult population attained a complete recovery. Old age patients benefited from the antidepressant treatment as much as the adult population, although therapeutic response may have a slower onset, and relapses are more frequent in elderly	3
Clomipramine	Kunik ME, Pollock BG, Perel JM, Altieri L. [24]	Tolerance and plasma levels monitoring	Patients with resistant depression, female, N=5	67-80 years old	HDRS, RSSE, clomipramine plasma concentration	HDRS scores decreased with 42%, and organic adverse events rate decreased with 57% (determined by RSSE score)	5
Dothiepin	Old Age Depression Interest Group [25]	Continuation/prophylaxis therapy	Double-blind, placebo controlled, 2 years, inclusion of patients with major depression, N=219	Not specified (old age)		Dothiepin decrease RR of relapse by 2.5 times. Previous severe somatic diseases, but no such disease present at the admission, associated with a more favorable prognosis. A prolonged major depressive episode must be treated for at least 2 years.	5
Duloxetine	Russell J, Rakin J, Wiltse C et al. [13]	Effects and tolerability of duloxetine in old age patients with MDD and comorbid anxiety symptoms	Multicentric, parallel groups, double blind, placebo controlled, N=311	>65 years old	HAMD17, GDS, VAS for pain symptoms, cognitive scales (VLRT, SDST, 2DCT, LNST), SF-36	Improvements of anxiety symptoms, Psychic Anxiety and Anxiety/Somatization. Therapeutic effect latency was 4-8 weeks on the Anxiety/Somatization scale. Significantly improvement of pain symptoms in patients with MDD.	5
Fluoxetine	Heiligenstein JH, Ware JE Jr, Beuerstein KM et al. [22]	Acute effects of fluoxetine vs. placebo over the global function and well being in old age depression	Randomized, 6 weeks, 261 fluoxetine treated patients, 271 with placebo	≥60 years old	SF-36	Patients receiving fluoxetine improved more than those with placebo in all scales, but significant results (p<0.05) were detected on mental health, role limitations due to emotional problems, physical functioning, somatic pain	4

LS= Level of significance; HAMD/HDRS= Hamilton Scale for Depression, SSI= Suicide Ideation Scale, PSWQ=Penn State Worry Questionnaire, BSI=Brief Symptom Inventory, CSDD= Cornell Scale for Depression in Dementia; CSRI= Costs-Client Service Receipt Inventory, IADL= Inventory of Activities of Daily Living, MADRS=Montgomery-Åsberg Depression Rating Scale, SSSEC=Symptom, Sign, Side-Effect Checklist, CGI-S= Clinical Global Impression- Severity, CGI-I= Clinical Global Impression-Improvement, QWB= Quality of Well-Being Scale, HR-QOL= Health Related Quality of Life, SCWT= Stroop Color-Word Test, SHQ= Suicidal History Questionnaire, MMSE= Mini-Mental Status Exam, MATTIS-DRS=MATTIS Dementia Rating Scale, GDS= Geriatric Depression Scale, RSSE= Rating Scale for Side Effects, VLRT=Verbal Learning and Recall Test, SDST= Symbol Digit Substitution Test, 2DCT= 2 Digit Cancellation Test, LNST= Letter-Number Sequencing Test  
MAOIs=monoaminoxidase inhibitors, ECT=electroconvulsant therapy, CR=controlled release, TCA= tricyclics, IPT=interpersonal therapy, SAE= Serious Adverse Event, AE= Adverse Event, MDD= Major Depressive Disorder

**Systematic reviews and meta-analyses** focused on pharmacologic therapy of major depression in elderly patients were extracted from the above mentioned databases, and a total number of 10 such researches resulted.

Geriatric psychotic depression responded in an equal manner to antidepressant monotherapy and to antidepressant+antipsychotic combination during the acute phase of treatment [31].

Pharmacologic treatment guided by an algorithm is superior to an individualized therapy, according to a systematic review, and the suggested phases of treatment are: 1- escitalopram (or sertraline/duloxetine); 2- switch on duloxetine (or venlafaxine/desvenlafaxine); 3- switch on nortriptyline (or bupropion); step 2-3 for partial response- augmentation using lithium or a typical antipsychotic (or SSRI/SNRI+mirtazapine/bupropion), and each step has a minimum duration of 6 weeks [32, 33].

There is a lower response rate to all antidepressants evaluated in male elderly patients, which are older, with a longer duration of the current episode, while a higher rate of response was observed in those with higher initial severity of depressive symptoms and in those with first depressive episode [34].

Duloxetine efficacy has been demonstrated during a systematic review, with an efficacy superior to placebo, and its comparison to SSRIs lead to the conclusion that duloxetine had a more favorable profile of adverse events, and also duloxetine is efficient on pain symptoms in elderly [35].

Recovering of elderly patients who were sufficiently treated (duration and doses) reaches a rate of 70% [36]. All antidepressant classes were more efficient than placebo in obtaining response, but for remission only when all the three classes were put together (SSRIs, tricyclics, other) a significant difference to placebo was obtained [37]. Another meta-analysis showed that antidepressants are more efficient in geriatric major depression (55+,  $p < 0.0001$ ), but in those with age of 65+ the efficacy is not enough proven due to a considerable heterogeneity of the results included in analysis [38]. An NNT of 14.4 was determined for an additional remission to an antidepressant versus placebo and NNT of 6.7 for the response to an antidepressant to placebo [37]. Another meta-analysis reports values for NNT of 3.6 for preventing a recurrence, NNT=2.9 for tricyclics and 4.2 for SSRIs [39].

Tricyclics and SSRIs had a similar efficacy over the HAMD scores, and a minimum 6 weeks are necessary for obtaining an optimum therapeutic effect [40]. Venlafaxine doesn't associate superior effects over HAMD compared to SSRIs or tricyclics [40]. According to a Cochrane review in population 65+ with major depression, OR values are 0.32 for tricyclics, 0.51 for SSRIs, and 0.17 for MAOIs [33].

**Table 2.** Systematic reviews and meta-analysis focused on old age depression treatment

Authors	Objectives	Design	Population	Results
Gournellis R, Oulis P, Howard R [31]	1. psychotic major depression in old age patients has a distinct overall severity comparative to non-psychotic major depression, beyond the presence of psychotic symptoms; 2. psychotic depression is a distinct clinical entity; 3. this pathology differs from psychotic major depression in young adults.	Literature systematic review	N=35 clinical trials included	No differences were detected regarding antidepressant efficacy used as monotherapy vs. antidepressant+antipsychotic combination during acute phase of treatment, but during maintenance phase there are some differences; many somatic complaints, hypochondriac and catastrophic delusions, but a lower level of anxiety comparative to younger adults; Patients diagnosed with psychotic major depression had a higher severity of depressive symptoms, more motor symptoms, guilt feelings, more depressive episodes with psychosis, more severe prognosis, severe dysfunction with frontal atrophy, lower level of beta-dopamine-hydroxylase activity.
Mulsant BH, Blumberger DM, Ismail Z, Rabheru K, Rapoport MJ [32]	Pharmacologic treatment guided by an algorithm (step-approach to old age depression treatment) is superior to an individualized treatment	Systematic literature review	Clinical guidelines, treatment algorithms	Step 1: escitalopram (as alternative-sertraline, duloxetine); step 2 for a minimal or absent response: switch on duloxetine (as alternative- venlafaxine, desvenlafaxine); step 3 for minimal or absent response- switch on nortriptyline (as alternative-bupropion). Step 2-3 for partial response: antidepressant augmentation with lithium or with an atypical antipsychotic (as alternative-SSRI/SNRI+mirtazapine/ bupropion). Each step duration- 6 weeks (range 4-8 weeks)
Calati R, Salvina Signorelli M, Balestri M et al. [34]	Antidepressant efficacy profile correlated with clinical features of depression and socio-demographic characteristics of old age population	Metaregression of double-blind, randomized trials in patients aged 60+, treated with any antidepressant for major depression; a number of 34 RCTs, meta-analyses and systematic literature reviews	MEDLINE, EMBASE, PsycINFO	Lower rate of response (MADRS, HAMD) was detected in all classes of antidepressants in male patients, older, prolonged duration of the current episode; higher rate of response in those with more severe initial symptoms and in those with first episode. Subgroups treated with an SSRI agent as monotherapy had similar results.
Del Casale A, Girardi P, Brugnoti R et al. [35]	Duloxetine efficacy in old age major depressive disorder	Systematic review	PubMed, PsycLIT, Embase	Duloxetine is safe and efficacious in this population, superior to placebo in all clinical trials, better differentiated from placebo comparative to SSRIs; duloxetine has a more unfavorable side events profile, comparative to SSRIs and a higher rate of discontinuation; duloxetine is efficient over pain in old age patients

Pharmacologic Treatment in Old-Age Major Depression:  
A Systematic Literature Review

Authors	Objectives	Design	Population	Results
Bottino CM, Barcelos-Ferreira R, Ribeiz SR [36]	Depression treatment in elderly depressed patients	Systematic review		70% of all the patients receiving enough treatment (duration and doses) recover from the depressive episode
Kok RM, Nolen WA, Heeren TJ [37]	Treatment efficacy in elderly	Systematic review and meta-analysis	N=51 RCTs, compared to N=29 RCTs double-blind	All antidepressant classes have been more efficient than placebo regarding obtaining of a response; if remission is the target, only considering all the 3 classes of studied antidepressants (SSRIs, tricyclics, other) showed a significant difference to placebo. NNT 14.4 (95% CI 8.3-50) for an additional remission with an antidepressant compared to placebo and NNT 6.7 (95% CI 4.8-10) for a therapeutic response
Kok RM, Heeren TJ, Nolen WA [39]	Continuation treatment in old age depression	Systematic review and meta-analysis	N=8 RCTs double-blind focused on maintaining and continuation of the antidepressant therapy in old age patients (n=925 subjects)	NNT for recurrence prevention is 3.6 (95% CI 2.8-4.8), NNT for tricyclics is 2.9 (95% CI 2.2-4.6), compared to NNT for SSRIs 4.2 (95% CI 3.2-5.9); tolerability similar between SSRIs and tricyclics
Mukai Y, Tampi RR [40]	Depression treatment in old age with single mechanism antidepressants versus dual mechanisms agents	Systematic review	≥59 years old, MDD, RCTs (n=18)	Tricyclics had a similar efficacy with SSRIs on HAMD scale. No supplemental benefits if venlafaxine is used, comparative to SSRIs or tricyclics on MADRS, HAMD or GDS.
Wilson K, Mottram P, Sivarathan A, Nightingale A [33]	Depression treatment in elderly	Cochrane review	>60 years old, N=17 trials that compared antidepressants and placebo (245 on tricyclics vs. 223 on placebo, 365 on ISRS vs. 372 on placebo, 58 on MAOIs vs. 63 on placebo)	MADRS, HAMD, other scales for depression; OR 0.32 (0.21, 0.47) for tricyclics, OR 0.51 (0.36, 0.72) for SSRIs, OR 0.17 (0.07, 0.39) for MAOIs. At least 6 weeks of treatment in order to obtain an optimal therapeutic response; few evidence for efficacy of low dose tricyclics
Tedeschini E, Levkovitz Y, Iovieno N et al [38]	Antidepressant efficacy in geriatric depression	Meta-analysis and meta-regression of placebo controlled RCTs	Comparison of patients aged <65 and ≥55. Results included 15 trials on old age depression and 59 trials on adult depression	Antidepressants were efficient in geriatric major depression (defined by onset in patients ≥55 years old, p<0.0001); efficacy has not been proven in patients ≥65 years old (p=.265); Heterogeneity is considered very high in reviewed trials results.

SSRI= selective serotonin reuptake inhibitor, SNRI=noradrenaline and serotonin reuptake inhibitor, RCT= randomized clinical trial

Integration of these results leads to the recommendations formulated in table 3. Each pharmacologic treatment is presented from an advantages/disadvantages analysis in elderly patients as they resulted from literature review.

**Table 3.** Grade Recommendation based on the literature review

Treatment	Clinical trials	Advantages/disadvantages	GRADE recommendation
SSRIs	[14-22], [26]	(+) paroxetine has been investigated in several trials that confirmed its efficacy; (+) citalopram, sertraline and fluoxetine also have been associated with favorable results (+) escitalopram (sertraline as alternative) is recommended by a meta-analysis as the first step in old age depression therapy (-) these agents may modify bleeding time, increase the risks for falls and fractures, SIADH, parkinsonism	<b>A</b> for paroxetine, sertraline, (es)citalopram, fluoxetine
SNRIs	[4], [9-11], [13], [40]	(+) venlafaxine is supported by the best evidence, including for patients who responded partially to other antidepressants (+) duloxetine is efficient in cases with anxiety and pain symptoms in geriatric depression (+) duloxetine has a tolerability profile superior to SSRIs according to a systematic review (-) High blood pressure as side event (-) efficacy similar to SSRIs	<b>A</b> for venlafaxine <b>B</b> for duloxetine (but <b>A</b> if anxiety /pain dominates)

Treatment	Clinical trials	Advantages/disadvantages	GRADE recommendation
Tricyclics	[9-11], [23-25], [40]	(+) nortriptyline has the most consistent evidence of efficacy from this class (+) nortriptyline plus lithium is an efficient option in cases of non-responsivity to other agents (-) no clear evidence for superior efficacy to SSRIs according to a systematic review (-) multiple cardiovascular, antihistaminic and anticholinergic adverse events	A for nortriptyline C for other tricyclics due to low tolerability issues
MAOI	[11], [28]	(-) efficacy inferior to venlafaxine/nortriptyline+lithium in patients who are non-responsive to other antidepressants	D
NaSSA	[26]	(+) efficacy similar to sertraline (+) proven efficacy to institutionalized patients aged 85+ (+) orodispersible formula has a proven efficacy, and this is important in subjects with deglutition difficulties (-) sedative properties	A

GRADE recommendations for level of evidence [41]:

- A = high quality data, future research would probably not change the recommendation's validity.
- B = moderate quality, future research will probably have an important effect in the appreciation of our trust in the recommendation.
- C = low quality, it's very probable that future research will have an important impact over our trust in the estimation of the effect and will very probably change the recommendation.
- D = high quality, any estimation of the effect is very uncertain.

## Conclusions

Data analysis is based on a relatively small number of trials, especially if we compare this number to the actually marketed antidepressants and to the importance of the geriatric depression.

Also, we detected very few head-to-head trials realized in this population, and this makes difficult to hierarchize antidepressant agents. This is not only a research problem in elderly population, and direct comparison studies on general population do not offer sufficient data to allow a stratified intervention based on efficacy.

Maximum GRADE recommendations are established for SSRIs (except for fluvoxamine, for which we don't have enough data), venlafaxine and nortriptyline. Duloxetine has a level B recommendation due to insufficient data, but if pain or anxiety dominates the clinical profile, recommendation gets a level A.

Mirtazapine has also a maximum level recommendation.

Other tricyclics except for nortriptyline must be recommended only with caution, due to low tolerability of these drugs in the old age population, even if the drugs are considered efficient.

MAOIs don't have enough support for making a recommendation in the treatment of geriatric depression, even in non-responsive forms, where venlafaxine/nortriptyline and lithium combinations are preferred.

In order to verify whether the drug works or not, the minimum duration of an antidepressant trial is 6 weeks. Response rate was smaller in all evaluated antidepressants in male patients, with more advanced age, longer duration of the current episode, but a higher rate of response was detected in those with higher initial severity of depressive symptoms and in those with first episode.

## References

1. Starkstein SE, Jorge RE, Mizrahi R, et al: The construct of minor and major depression in Alzheimer's disease. *Am J Psychiatry* 2005; 162:2086–2093.
2. Williams JWJ, Barrett J, Oxman T, et al: Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA* 2000; 284:1519–1526.
3. Barak Y, Olmer A, Aizenberg D. Antidepressants reduce the risk of suicide among elderly depressed patients. *Neuropsychopharmacology*. 2006;31(1):178–181.
4. Crumacker DW. Suicidality and antidepressants in the elderly. *Proc (Bayl Univ Med Cent)* 2008; 21(4):373-377.
5. Erikson EH. *The life cycle completed (Extended version)*. W.W. Norton & Co. Ed., New York, 1998.
6. Neugarten B. Age groups in American society and the rise of the young-old. *Annals of the American Academy of Political and Social Science*. 1974; 415:187–198.
7. Definition of an older or elderly person. Accessed at <http://www.who.int/healthinfo/survey/ageingdefnolder/en/> on 22/02/2016, 00:57.
8. Joel J, Begley AE, Mulsant BH et al. Dynamic prediction of treatment response in late-life depression. *Am J Geriatr Psychiatry* 2014;22(2):167-76.
9. Kok RM, Aartsen M, Nolen WA, Heeren T. The course of adverse effects of nortriptyline and venlafaxine in elderly patients with major depression. *J Am Geriatr Soc* 2009;57(11):2112-7.
10. Kok RM, van Baarsen C, Nolen WA, Heeren TJ. Early response as predictor of final remission in elderly depressed patients. *Int J Geriatr Psychiatry* 2009;24(11):1299-303.
11. Kok RM, Nolen WA, Heeren TJ. Outcome of late-life depression after 3 years of sequential treatment. *Acta Psychiatr Scand* 2009;119(4):274-81.
12. Hardy BG, Shulman KI, Zuccherro C. Gradual discontinuation of lithium augmentation in elderly patients with unipolar depression. *J Clin Psychopharmacol* 1997; 17(1):22-6.
13. Russell J, Raskin, Wiltse C et al. Efficacy and Tolerability of duloxetine treatment in elderly patients with major depressive disorder and concurrent anxiety symptoms. *Psychiatry (Edgmont)* 2007; 4(6):33-45.
14. Gibiino S, Mori E, De Ronchi D, Seretti A. Potential benefits of slow titration of paroxetine treatment in an elderly population: eight week results from a naturalistic setting. *J Clin Psychopharmacol* 2013; 33(40):565-9.
15. Rapaport MH, Lydiard RB, Pitts CD et al. Low doses of controlled-release paroxetine in the treatment of late-life depression: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2009; 70(1):46-57.

16. Dombrovsky AY, Lenze EJ, Dew MA, et al. Maintenance treatment for old-age depression preserves health-related quality of life: a randomized, controlled trial of paroxetine and interpersonal psychotherapy. *J Am Geriatr Soc* 2007; 55(9):1325-32.
17. Reynolds CF 3rd, Dew MA, Pollock BG et al. Maintenance treatment of major depression in old age. *N Engl J Med* 2006; 354(11):1130-8.
18. Burrows AB, Salzman C, Satlin A et al. A randomized, placebo-controlled trial of paroxetine in nursing home residents with non-major depression. *Depress Anxiety* 2002; 15(3):102-10.
19. Sneed JR, Roose SP, Keilp JG et al. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry* 2007;15(7):553-63.
20. Roose SP, Sackeim HA, Krishnan KR et al. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am J Psychiatry* 2004; 161(11):2050-9.
21. Oslin DW, Ten Have TR, Streim JE et al. Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. *J Clin Psychiatry* 2003; 64(8):875-82
22. Heiligenstein JH, Ware JE Jr, Beusterien KM et al. Acute effects of fluoxetine versus placebo on functional health and well-being in late-life depression. *Int Psychogeriatr* 1995; 7(Suppl.):125-37.
23. Reynolds CF 3rd, Frank E, Kupfer DJ et al. Treatment outcome in recurrent major depression: a post hoc comparison of elderly („young old”) and midlife patients. *Am J Psychiatry* 1996; 153(10):1288-92.
24. Kunik ME, Pollock BG, Perel JM, Altieri L. Clomipramine in the elderly: tolerance and plasma levels. *J Geriatr Psychiatry Neurol* 1994; 7(3):139-43
25. Old Age Depression Interest Group. How long should the elderly take antidepressants? Double-blind placebo-controlled study of continuation/prophylaxis therapy with dothiepin. *Br J Psychiatry* 1993; 162:175-82.
26. Banerjee S, Hellier J, Romeo R et al. Study of the use of antidepressants for depression in dementia: the HTA-SADD trial- a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. *Health Technol Assess* 2013; 17(7):1-166.
27. Nelson JC, Hollander SB, Betzel J et al. Mirtazapine orally disintegrating tablets in depressed nursing home residents 85 years of age and older. *Int J Geriatr Psychiatry* 2006; 21(9):898-901.
28. Kok RM, Vink D, Heeren TJ, Nolen WA. Lithium augmentation compared with phenelzine in treatment-resistant depression in the elderly: an open, randomized, controlled trial. *J Clin Psychiatry* 2007; 68(8):1177-85.

29. Reynolds CF 3rd, Butters MA, Lopez O et al. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. *Arch Gen Psychiatry* 2011; 68(11):51-60.
30. Karlsson I, Godderis J, Augusto de Mendoca Lima C et al. A randomized, double-blind comparison of the efficacy and safety of citalopram compared to mianserin in elderly, depressed patients with or without mild to moderate dementia. *Int J Geriatr Psychiatry* 2000; 15(4):295-305.
31. Gournellis R, Oullis P, Howard R. Psychotic major depression in older people: a systematic review. *Int J Geriatr Psychiatry* 2014; 29(3):789-96.
32. Mulsant BH, Blumberg DM, Ismail Z, Rabheru K, Rapoport MJ. A systematic approach to the pharmacotherapy of geriatric major depression. *Clin Geriatr Med* 2014; 30(3):517-534.
33. Wilson K, Mottram P, Sivaranthan A, Nightingale A. Antidepressant versus placebo for depressed elderly. *Cochrane Database Syst Rev* 2001; (2):CD000561.
34. Calati R, Salvina Signorelli M, Balestri M et al. Antidepressants in elderly: meta-regression of double-blind, randomized clinical trials. *J Affect Disord* 2013; 147(1-3):1-8.
35. Del Casale A, Girardi P, Brugnoli R et al. Duloxetine in the treatment of elderly people with major depressive disorder. *Riv Psichiatr* 2012; 47(6):479-488.
36. Bottino CM, Barcelos-Ferreira R, Ribeiz SR. Treatment of depression in older adults. *Curr Psychiatry Rep* 2012; 14(4):289-97.
37. Kok RM, Nolen WA, Heeren TJ. Efficacy of treatment in older depressed patients: a systematic review and meta-analysis of double-blind randomized controlled trials with antidepressants. *J Affect Disord* 2012; 141(2-3):103-15.
38. Tedeschini E, Levkovitz Y, Iovieno N et al. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trial. *J Clin Psychiatry* 2011; 72(12):1660-8.
39. Kok RM, Heeren TJ, Nolen WA. Continuing treatment of depression in the elderly: a systematic review and meta-analysis of double-blinded randomized controlled trials with antidepressants. *Am J Geriatr Psychiatry* 2011; 19(3):249-55.
40. Mukai Y, Tampi RR. Treatment of depression in the elderly: a review of the recent literature on the efficacy of single-versus dual-action antidepressants. *Clin Ther* 2009; 31(5):945-61.
41. GRADE Recommendations. Accessed at [www.gradeworkinggroup.org](http://www.gradeworkinggroup.org) in 02/07/2016, 12:35.

## A COMPARISON OF VALPROATE'S EFFECT VERSUS CARBAMAZEPINE IN PROPHYLACTIC TREATMENT OF BIPOLAR PATIENTS - AN ALBANIAN EXPERIENCE

Fatime Elezi<sup>1</sup>, Eugjen Sotiri<sup>1</sup>, Sonila Tomori<sup>2\*</sup>, Ardian Braho<sup>1</sup>, Lefter Sinani<sup>1</sup>, Elizana Petrela<sup>3</sup>

<sup>1</sup>University Hospital Center "Mother Teresa", Neuroscience Department, Psychiatric Service, Tirana, Albania

<sup>2</sup>University Hospital Center "Mother Teresa", Department of Pediatrics, Neuropediatric Unit, Tirana, Albania

<sup>3</sup>Tirana University of Medicine, Statistical Department University Hospital Center "Mother Teresa", Tirana, Albania

### **Abstract**

*Introduction: Bipolar disorder (manic-depressive illness) is a chronic, cyclic disease that afflicts approximately 1% of the population. This illness frequently begins in the teen years but often escapes diagnosis at this time because episodes are misinterpreted as conduct disorder, schizophrenia, depression, or other disorders. Carbamazepine and valproate are used in the treatment of acute bipolar mania and as maintenance treatments for disorders.*

*Aims: To compare the efficacy of valproate versus carbamazepine in the prophylactic treatment of patients with bipolar disorders.*

*Method: We studied 120 patients with at least two episodes of bipolar disorder (DSM-IV). This is a randomized, prospective clinical trial with duration of 2 years, two equal parallel-groups with open label pre-randomized phase. Primary outcome measure was time to relapse/recurrence to any mood episodes and survival analyses were performed.*

*Results: Cumulative survival for valproate group was 26% higher than carbamazepine group, while mean and median survival time were respectively 35% and 53% longer for valproate. Carbamazepine showed approximately the same effect as valproate in some subtypes of bipolar disorders and with co-morbidity.*

*Conclusions: Valproate is significantly more effective than carbamazepine in prophylactic treatment of bipolar disorders.*

**Keywords:** bipolar disorder, carbamazepine, valproate, survival analysis.

### **Introduction**

Bipolar disorder or manic-depressive is a cyclic and chronic illness characterized by deep depressive periods alternated with manic/mixed/hypomanic episodes. The prevalence of bipolar disorder is estimated to be relatively small. The lifetime prevalence rate of bipolar I is approximately 1.0%, for bipolar –II is 1.1%, and 2.4% for bipolar threshold. Some studies suggest a

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\* Correspondence: Sonila Tomori, e-mail: sonila.tomori@gmail.com.

lifetime prevalence of bipolar disorder in general population between 1-3% [1]. On the other hand the lifetime prevalence rates of major depressive disorder were a lot higher reaching 16.2%. However, the bipolar disorders were found to be much more persistent than major depressive disorders. Therefore, bipolar disorders may not be as prevalent as major depression but appear to be more persistent and chronic. In general, bipolar disorder affects equally males and females in every life stage, from 13-15 years old to over 60 years old, with a mean age of onset of 20-30 years old and a second peak of onset 40 years old [2]. For bipolar I disorder there is an almost equal prevalence of the disorder across males and females unlike major depressive disorders where there is a higher female to male ratio. Due to the higher prevalence of major depressive disorder in women it is obvious that there is a slightly higher prevalence of bipolar II disorders in women. Early onset of bipolar disorder sometimes can lead to misdiagnose or under diagnose of it, because of misinterpretation of clinical signs as conduct disorder, schizophrenia, depression or other disorders. It is known that the course of bipolar disorder is unpredictable so the treatment is complex and includes biological strategies and psychological interventions.

The pharmacological treatment of BD passes through three phases:

*Acute treatment phase* refers to the period from beginning of the treatment until remission of initial symptoms which lasts 2-10 weeks. *Continuous treatment phase* or stabilized phase refers the period of treatment's continuation to prevent emerging of relapse, which means the full reduction of initial symptoms with duration of 6 months. *Maintenance treatment phase* refers further continuation of medical treatment to prevent the appearance of recurrence (new episodes).

Meanwhile the long-term treatment phase refers the reduction of intensity of symptoms and frequency of recurrence or complete prevention, which means prophylactic treatment [3,4].

Although the term prophylactic is not a well précised, in our study we agreed to use the term prophylactic treatment meaning both continuous and maintenance treatment. **Mood stabilizers:** Lithium and Carbamazepine are considered as basic drugs to be used in treatment of BD in acute and prophylactic phases, treating both manic and depressive episodes (5). In recent studies is found that some other antipsychotics and anticonvulsivants (olanzapine, quetiapine, aripiprazole, valproate, lamotrigine, gabapentine) have shown a good response in acute treatment and prophylaxis. It is found that valproate has similar effect as lithium of bipolar spectrum with a light superiority in treatment of sub-types of bipolarity especially in rapid cycling mixed statues and in co-morbidity with substance use or other psychiatric disorders [6,7,8].

## **Aims**

To compare the efficacy of Valproate versus Carbamazepine in the prophylactic treatment of patients with bipolar disorders.

## Objective

To measure the effect of valproate and carbamazepine and to obtain the effect's difference in efficacy between them when used as prophylactic drugs in bipolar patients.

## Methods

This is a 2 years open comparative and randomized longitudinal prospective clinical trial, with two parallel groups (no=60) and a pre-randomized treatment phase with duration of 2-8 weeks. The sample size is 120 patients (after randomized phase) defined to provide power effect of 80% (with  $\alpha=0.05$ ) to obtain 20% absolute improvement of survival time to relapse/recurrence.

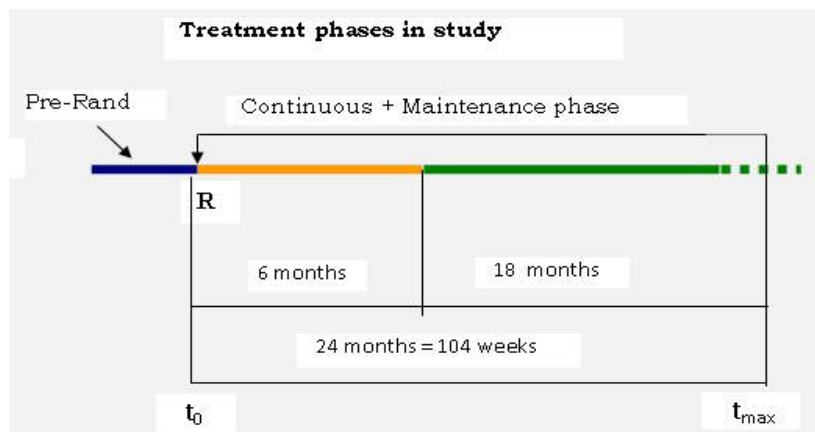
**Inclusion criteria:** Patients 19–65 years old, with classical bipolar I disorder (recent manic and depressive episode without psychotic features); non-classical bipolar I disorder (recent manic and depressive episode with psychotic features); bipolar I disorder mix-episode, bipolar I disorder rapid cycling type, bipolar II disorder with recent depressive episode or hypomania; bipolar II disorder rapid cycling type; bipolar I and II disorder with moderate to severe gravity, with at least two episodes (in order to require long-term treatment); with or without treatment prior to the study.

**Exclusion criteria:** patients with not otherwise specified bipolar disorder, bipolar disorder due to other medical conditions, cyclothymic disorder, mild bipolar I and II disorders or in partial remission, and pregnant women or during lactation period.

### Recruitment, Open Phase (pre-randomized)

Patients were selected according to DSM-IV criteria for bipolar disorder and required a long-term treatment (n=194), male and female, in age interval 19-65 years, presented at Psychiatric Service, Emergency Ward (UHC “Mother Teresa” Tirana) [20]. All of them had more than two mood episodes during the time prior to our study, and severity levels from moderate to severe according to standard rating scales CGI 4-7, GAF, HAM-D-RS and MRS [9,10,11,12]. A comprehensive psychiatric and physical examination was performed to all patients to exclude all possible organic illness. Patients that fulfilled the inclusion criteria entered in the acute treatment phase of the study. Assessment during the *acute phase* is done every 2 weeks. All patients that resulted with CGI efficacy index of 4-5 (cut-off) and CGI improvement of 2-3 (cut-off) entered to the next phase. The main treatment for patients during the long-term phase (continuous & maintenance) included valproate (Vp) and carbamazepine (Cbz). Drug selection during this phase is decided following the clinical guidelines, as by diagnosis and types of mood episodes determined at the beginning of the study. *Continuous phase* starts when is achieved the positive outcome from the acute phase and it lasts 6 months. During follow up visits there are performed some measures such as events: time to relapse; time to discontinuation of treatment (side effects, negative compliance, or other reasons); time loosing the study. Patients that relapsed, discontinued the treatment or lost to follow-up were excluded from the study. *Maintenance*

*phase* extends from the end of continuous phase till the end of follow-up period that lasted 18 months. In this phase all patients continued the mono-therapy treatment with mood stabilizers pointed during randomizing process. During this phase the assessment was performed each three months and measured these events: time to recurrence; time to discontinuation of treatment (side effects, negative compliance, or other reasons); time loosing the study. Patients that did not experience recurrence until the end of study are considered as right censored.



**Figure 1.** Treatment phases in study

*Main Measure of results* is the time to relapse or to recurrence of any mood episode.

**Statistical analyses:** Survival analysis is the suggested method in clinical trials with long-term treatment [13,14]. The result evaluation in survival analysis is done using the *Survival Cumulative Probability* referred as survival function ( $S(t)$ ), in any point of time of the study as well as median time, that is time to survive for half of the sample [21,22].

In evaluation of predictors influence to treatment response statistical significance is defined to 95% ( $p < 0.05$ ). Statistical analysis is performed using the SPSS for Windows (Kaplan Meier and Cox regression).

**Safety:** All patients were involved voluntarily in the study.

**Declaration of interest:** the study is completed without any interest.

## Results

### *Descriptive analysis – demographic data*

In the study were randomized 120 patients, 59.2% of them female, with high school degree 60.8% and university degree 9.2%. The predominant age of sample were 26-35 years old (33,3%) and other group 36-45 years old (30%). The marital status was 59.2% married, 36.7%, unmarried, 4.2% were divorced/widowed. The employment situation was: 30.8% employed; 60% unemployed and 9.2% were retired or disabled. **Clinical Characteristics:** the patients in study were diagnosed with: a classical bipolar I disorder 35.8%, non-classical bipolar I disorder 21.7%, bipolar I disorder mix-

episode 22.5%, bipolar I disorder rapid cycling type 8.3%. While with bipolar II disorder were 9.2% and bipolar II disorder rapid cycling type were 2.5%.

Using another way of grouping the sample was by categorizing as classic bipolar I disorder and non classic bipolar I disorder, it resulted respectively 36.7% and 63.3%. The majority of patients during the open phase were in manic episode with or without psychotic features 45.8% and with mixed episode 22.5%, while with hypomania only 9.2% of them. Psychiatric co-morbidity was 32.5% and presence of significant life stressors were in 56.7% of the entire sample (in both parallel groups of the study).

Reasons for study exit by groups were:

- Cbz group 20% relapsed, 55% recurred, side effects 11.7%, treatment's discontinuation 3.3%, lost from follow up 1.7% and survived 8.3%;
- Vp group 10% relapsed, 48.3% recurred, 5% had side effects, treatment's discontinuation 3.3%, lost from follow up 1.7% and survived 31.7%.

*Side effects for Cbz group* were: hyper-transaminasemia for 2 patients occurred in 14th and 43rd week, alopecia in two patients occurred in 22nd and 24th week, skin rash in three patients occurred in 42nd week together with tremor and sedation in 18th week and vomiting in 10th week. *Side effects for valproate group* were: hyper-transaminasemia in 1 patient during 26th week, weight gain in 2 patients during 36th and 48th week. One of the female patients had a recurrence in 57th week of the study and at the same time was diagnosed with polycystic ovarian. Finally we must conclude that survived patients in Cbz group were 8.3% and in Vp group were 31.7%; had relapse/recurrence in Cbz group 75% and in Vp group 58.3%; while censored in Cbz group were 16.7% and in Vp group were 10%.

### Statistical Analysis – Survival Analysis with Kaplan-Meier Method

The survival event for the dependent variable Time to Relapse/Recurrence/Censored for Carbamazepine group is demonstrated in Tables 1 and 2.

**Table 1.** Survival event for carbamazepine group

Cases	Censored	Events	Survival S(104)	Standard Error
60	16 (26.67%)	44	9.71%	3.7

**Table 2.** Mean and median time for carbamazepine group

	Survival Time	Standard Error	95% Confidence Interval
Mean	54	4	(47 - 62)
Median	51	6	(40 - 62)

The survival event for the dependent variable Time to Relapse/Recurrence/Censored for Valproate group is demonstrated in Table 3 and 4.

**Table 3.** Survival event for valproate group

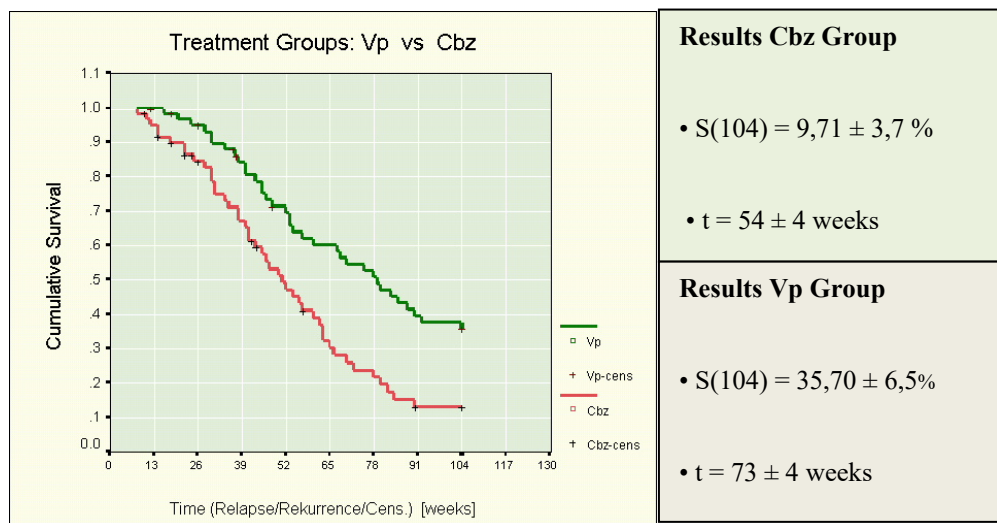
Cases	Censored	Events	Survival S(104)	Standard Error
60	25 (41.67%)	35	35.70%	6.5

**Table 4.** Mean and median time for valproate group

	Survival Time	Standard Error	95% Confidence Interval
<b>Mean</b>	73	4	(66 - 81)
<b>Median</b>	79	9	(62 - 96)

It is clear that time to survival was longer in valproate group with mean and median time respectively 73 weeks and 79 weeks compared to Cbz group table 1 and 2.

The difference effect between valproate and carbamazepine by using cumulative survival showed a distinctive difference in effect with superiority of valproate versus carbamazepine and with a decline effect of carbamazepine after the first year of treatment. We found that these differences are related not only with survival time but also with mean and median time to relapse and recurrence. It resulted that in patients that were treated with Vp recurrence had happened in  $73 \pm 4$  weeks (mean time) and in  $79 \pm 6$  weeks (median time) while in patients treated with Cbz it happened in  $54 \pm 4$  weeks (mean time) and in  $51 \pm 6$  weeks (median time) – Figure 2.



**Figure 2.** Curves and results of cumulative survival for both groups

### Survival difference between two treatment groups

Null hypothesis testing procedure was performed using the Log-Rank and Breslow (Wilcoxon) tests. (Table 5).

**Table 5.** Survival differences between two groups

	Statistical value	Freedom interval	P-Value
<b>Log Rank</b>	10.75	1	.0010
<b>Breslow</b>	9.92	1	.0016

Both methods used to test the null hypothesis give statically significant argument to refuse the hypothesis, so the null hypothesis in comparison of both treatment groups with Vp and Cbz shows statistically significant difference in effects to time of relapse/recurrence.

**The absolute difference of survival of Vp group versus Cbz group:**

$$S(104)_{Vp} - S(104)_{Cbz} = 0.3570 - 0.0971 = 0.2599 = 0.26, \text{ or } 26\%$$

Notice that this difference in effect was statistically significant, Log-Rank,  $p = 0.0010$

It can be stated that Vp provides a survival 26.67% higher than Cbz to relaps and recurrence in long term treatment of bipolar patients.

**The difference of effect based on mean and median time to survival:**

Valproate resulted to extend the mean time to survival (*the time of wellbeing without any relapse or recurrence*) 35% or 19 weeks longer than Cbz.

Valproate resulted to extend the median time to survival (*the time of wellbeing without any relapse or recurrence*) 53% or 28 weeks longer than Cbz.

**The relative difference of hazard ratio to relapse/recurrence of Cbz group versus Vp group tested with Cox Regression method:**

**Table 6.** Codification of categorical variables

		Frequency	(1)
Treatment in Study	1=Cbz	60	1.000
	3=Vp	60	.000

**Table 7.** Variables in equation

Treatment in study	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
	.735	.230	10.189	1	.001	2.085	1.328	3.273

It resulted that treatment with Cbz versus treatment with Vp has a higher hazard ratio to relapse /recurrence by 2,085 times or 108.5% ( $B = 0.735, p = 0.001$ ) – Table 7.

**Discussion**

This is a 2 years open comparative and randomized longitudinal prospective clinical trial, with two parallel groups and a pre-randomized treatment phase with duration of 2-8 weeks. Through this comparison study we aimed to evaluate the effects of anticonvulsivant in the treatment of BD especially to find out the valproate’s effect as a new treatment for bipolar patients versus carbamazepine. Although we aimed to further contribute in improvement of treatment guidelines for bipolar disorder in Albania.

The cumulative survival found by our study in Cbz group for 2 years was 9.71%. Keck at al (2002) suggests an outcome of  $\leq 25\%$  in one year, while Hartong et al (2003) [15] found a survival for the

Cbz group 32% in two years. Other authors have found a survival of 4% in Cbz group in one year Denicoff et al (1997) [16] and 47 % in one year Solomon et al (1997) [17]. It can be said that the result found while reviewing the literature by Hartong with 32% survival in 2 years differs significantly from our findings (it is 22.29% times higher). It is logical to assume that this difference was influenced by clinical characteristics of patients in both studies; Hartong have included only the patients without prior treatment with mood stabilizers (treatment naive), while the result of Denicoff study was designed just for manic patients.

The cumulative survival found by our study in Vp group was 35.70% during 2 years prophylactic treatment. Very few similar studies found the cumulative survival in patients treated with valproate as follows: Bowden et al (2000) cumulative survival in one year 41% [18] while Keck et al (2002) cumulative survival 25% in one year. We should consider our results as satisfying and similar with Bowden study, which has been considered a clinical study with a good and rigorous methodology [19]. In our study the survival analysis to relapse/recurrence resulted in significant difference between two groups with 26% in favor to valproate and a P-value = 0.0010.

By a careful observation it is easily noticeable the difference of effects between two treatment groups. So, we found a deep distinction in effects of valproate versus carbamazepine, with decline of Cbz prophylactic effect after the first year.

## Conclusions and Recommendations

Valproate is an effective mood stabilizer when used as prophylactic drug in bipolar patients. Valproate is superior versus carbamazepine as monotherapy in long term treatment of spectrum bipolar disorders. Carbamazepine seems to decline the long term therapeutic effect after the first year of treatment. Valproate is well tolerated than carbamazepine and its pharmacological ensures an adequate duration of the long term treatment.

The anticonvulsivant drug Valproate has proven to be effective as mood stabilizer in prophylactic treatment of bipolar patient. During the long term treatment should be attentive to consider adverse effects of valproate and Cbz and to address them properly.

### Abbreviations:

DSM-IV:	Diagnostic Statistical Manual - IV
Carbamazepine:	Cbz
Valproate:	Vp
CGI	Clinical Global Impression
GAF	Global Assessment of Functioning
HAMD-RS	Hamilton Depression Rating Scale
MRS	Mania Rating Scale

## References

1. Weissman (2002) Clinical Practice Guideline for the Treatment of Bipolar Disorder in Adults, first edition, Features of Bipolar Disorders, Epidemiologia, Clinical Presentationes and Prognosis: 1-100.
2. Angst J, Bowden L.C et al (2001) Guidelines for Investigating Efficacy in Bipolar Disorder European Neuropsychopharmacology 11 79–88; ECNP Consensus Meeting March 2000 Nice. [www.elsevier.com](http://www.elsevier.com)
3. Sachs GS, Rush AJ (2003) Response, remission, and recovery in bipolar disorders: what are the realistic treatment goals? Journal Clinical Psychiatry. 64 suppl 6:18-22 .
4. National Institutes of Health Consensus Development Conference Statement: (1984). Mood Disorders: Pharmacologic Prevention of Recurrences. NIH Consens Statement 1984 Apr 24-26; 5(4):1-23.
5. Stern Th.A. M.D., et al (2001) Bipolar Disorder, Nidus Information Services New York, [www.well-connected.com](http://www.well-connected.com)
6. Kim S., et al (2000) Management of Bipolar Disorder Ammerican Family of Physician; 62: 1343-53, 1357-8.
7. Frances A, Docherty JP, Kahn DA: (1996) The Expert Consensus Guideline Series: Treatment of Bipolar Disorder. Journal Clinical Psychiatry; 57(Dec suppl A):1-88.
8. Stahl S.M., (2000) Essential Psychopharmacology of depression and Bipolar Dissorder. Chap. 3 New antidepressants and mood stabilizers. 111-163.
9. Guy W, Bonato RR (1970) National Institute of Mental Health. CGI: Clinical Global Impressions. Manual for the ECDEU Assessment Battery.2. 12-1-12-6.
10. Waldinger R.J. M.D (1997) Psikiatria për studentët e mjekësisë, Përkthyer dhe redaktuar nga Dr. Anastas Suli (1999) 117-165.
11. Hamilton M. (1960) A rating scale for depression. J Neurol Neursurg Psychiatry. 23:56-62.
12. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978; 133:429-435.
13. Sachs GS, et al, (2000) The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder Postgrad Med Special Report 1-104.
14. Calabrese R.J, et al (2001) Evolving methodologies in bipolar disorder maintenance research. BJP 178: s 157-s 163.
15. Hartong EG, et al. (2003) Prophylactic efficacy of lithium versus carbamazepine in patients in the treatment-naïve bipolar patients. Journal Clinical Psychiatry February; 6(2):144-51.

16. Denicoff KD, et al (1997) Comparative prophylactic efficacy of lithium and carbamazepine the combination in bipolar disorder. *Journal Clinical of Psychiatry*; Nov 58(11):470-8.
17. Solomon DA et al (1997) A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. *Journal Clinical of Psychiatry*; 58:95-99.
18. Bowden et al (2000) A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Divalproex Maintenance Study Group*.
19. Keck PE, et al (2002) Carbamazepine and valproate in the maintenance treatment of bipolar disorder. *Journal Clinical of Psychiatry*; 63(suppl 10):13-17.
20. American Psychiatric Association, (1994) *Diagnostic and Statistical Manual*; 317-391
21. What is Power Analysis? [www.PowerAnalysis.com](http://www.PowerAnalysis.com)
22. Power Analysis for Survival Analysis. Software Power and Precision. [www.PowerAnalysis.com](http://www.PowerAnalysis.com)

## ASSESSMENT OF CARDIOVASCULAR RISK IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

Veronica Rusanu<sup>1\*</sup>, Johanna C. Popescu<sup>2</sup>, Roxana M. Stoean<sup>3</sup>, Claudia Chivu<sup>4</sup>,  
Brindusa E. Focseneanu<sup>5</sup>, Bogdan E. Patrichi<sup>6</sup>, Mirela Manea<sup>7</sup>

<sup>1</sup>Senior Psychiatrist, Clinical Emergency Hospital Bucharest, PhD student, “Carol Davila”  
University of Medicine and Pharmacy, Bucharest, Romania

<sup>2</sup>Social Worker at Rahova Penitentiary Bucharest, Romania

<sup>3</sup>Senior Psychiatrist, Clinical Emergency Hospital “Sf. Pantelimon” Bucharest, Romania

<sup>4</sup>MD at “Prof. Dr. Al. Obregia” Psychiatric Hospital in Bucharest, Romania

<sup>5</sup>Senior Psychiatrist, PhD, Assistant Lecturer “Titu Maiorescu” University of Medicine Bucharest

<sup>6</sup>Senior Psychiatrist, PhD “Carol Davila” University of Medicine and Pharmacy, Bucharest

<sup>7</sup>Senior Psychiatrist, Professor “Carol Davila” University of Medicine and Pharmacy, Bucharest

### **Abstract**

*Introduction: Each year, cardiovascular diseases (CVD) determine over 4 million of deaths in Europe from which over 1.9 million of them are in the European Union. Determination of the cardiovascular rhythm establishes the probability that a person experiments a cardiovascular event in a certain period of time, usually 5-10 years. The objective of the present study is to evaluate the risk of death by cardiovascular disease in the following 10 years using the SCORE index in patients diagnosed with a disorder of schizophrenic spectrum with the duration of the psychiatric disease of at least 10 years compared to patients with the same diseases, but diagnosed for maximum 2 years.*

*Methods: We included patients with ages between 40-65 years diagnosed with a disorder of the schizophrenic spectrum: schizophrenia, schizoaffective disorder, delirious disorder, schizophreniform disorder, short psychotic disorder. The I-B group consisted of patients with a history of the disease of maximum 2 years and the II-B group included patients with a history of minimum 10 years of the disorder.*

*Results: Patients in the group with a long course of disorder have significantly higher levels of cholesterol, triglycerides and BMI compared to the patients with a course of disorder of maximum 2 years. Moreover, the calculated SCORE index is significantly higher in the same group of patients.*

*Conclusion: The research emphasizes a tendency of increasing the factors value which is a risk for developing a CVD, in the patients' group with a disorder course of minimum 10 years, which imposes a serious management of the risk factors.*

**Keywords:** schizophrenia spectrum disorders, SCORE, cardiovascular risk.

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\* Correspondence: Veronica Rusanu, e-mail: veronicarusanu@yahoo.com.

## Introduction

Each year, CVD determines over 4 million of deaths in Europe from which over 1.9 million of them are in the European Union, according to the statistic data provided by European Heart Network and European Society Cardiology in the report from 2012 and available on the website <http://www.chnheart/> [1]

The European Guide for Preventing Cardiovascular Diseases in the Clinical Practice, drafted by the European Society of Cardiology together with other societies of preventing cardiovascular diseases confirm again the fact that the cardiovascular diseases are the main cause of premature death in Europe. Death by CVD occurs often suddenly, before assuring the access to medical assistance, what makes the therapeutic intervention to be inapplicable or palliative. The CVD appearance is highly correlated with the lifestyle and with the physiological or biochemical factors on which it can be intervened with the purpose of reducing the mortality and morbidity through CVD. Subjacent atherosclerosis develops slowly, during a lot of years, and when the symptomatology appears it is usually advanced [2].

Determination of the cardiovascular rhythm establishes the probability that a person experiments a cardiovascular event in a certain period of time, usually 5-10 years. By cardiovascular event it is understood the ischemic heart disease, cerebrovascular disease or peripheral arterial disease, aortic aneurysm, generally all the diseases which suppose an atherosclerotic cause [3].

The patients with psychotic disorders have a rate of increased mortality [4]. The premature death is caused by suicide, but also by diseases like CVD, diabetes mellitus, pulmonary disorders etc. [5]. Compared to the general population, the patients with disorders of schizophrenic spectrum have and increased risk of obesity, diabetes and smoking [6].

The SCORE system calculates the probability of death by cardiovascular event, in the following 10 years. It is easy to be calculated and it takes into account the following parameters: sex, age, smoking, arterial pressure value and total cholesterol value [7]. Romania uses the diagram with increased risk. Generally, a value higher than 5% is considered a high risk. If the subjects have a sedentary lifestyle, they are fat, have increased values of triglycerides or have a poor social status, the risk can be bigger than the one indicated by the diagram. The diabetes mellitus presence increases the risk 5 times. Figure 1 presents the SCORE diagram.

The SEPHAR study has emphasized that the mean value of the death risk due to cardiovascular cause on a period of 10 years, estimated according to the SCORE system, in Romania at the adult population level, is of 3.5%. The male subjects have presented a significant higher risk compared to the female patients. Almost 1 of 5 interviewed subjects have a risk higher  $\geq 5\%$ , but scores of higher risk  $\geq 15\%$  have been observed only at the male subjects and have represented 4% from the total [8, 9].

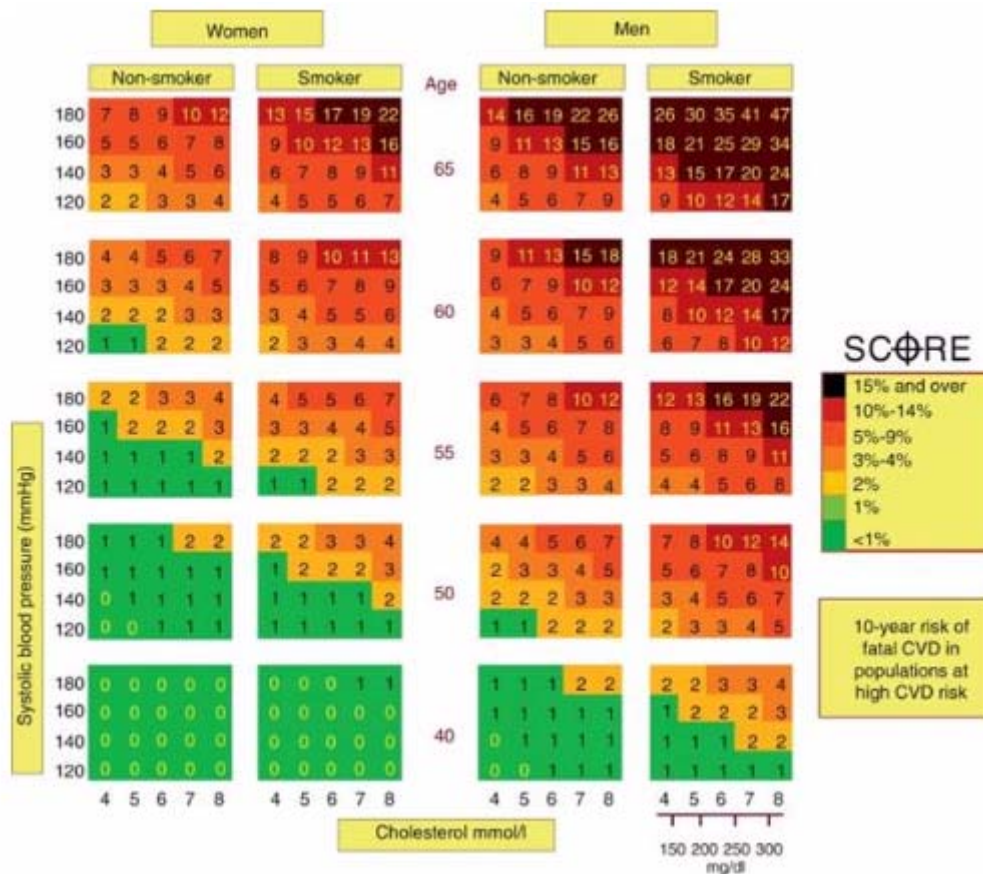


Figure 1. SCORE diagram

The present study evaluates the risk of death by cardiovascular disease in the following 10 years using the SCORE index in patients diagnosed with a disorder of schizophrenic spectrum with the duration of the psychiatric disease of minimum 10 years compared to patients with the same diseases, but diagnosed for maximum 2 years. It is known the fact that most of the patients with psychiatric diseases have a reduced social-economic status, are socially isolated, are subjected more to stress and have customs of unhealthy life (70% of them smoke), experience frequently negative emotions as depression or hostility [10]. All these can be an obstacle in maintaining a healthy life style, thing which, together with the negligence of the health condition in general, with the secondary effects of the psychotropic medication, especially the dysmetabolic syndrome, increases the risk of appearance of some cardiovascular events which can determine a premature death. Together with the developed cardiovascular disease, for patients with disorders from the schizophrenic spectrum the change of the lifestyle is difficult: for example, he barely participates to the programs of secondary prevention which suppose the performance of physic exercises or maintenance of an equilibrated diet which determines losing weight, quitting smoking [11]. The main purpose of the paper was to emphasize if the prolonged evolution (minimum 10 years) of some psychotic disease, of schizophrenic spectrum, attires in somatic plan a series of risks, especially that of death by events of cardiovascular nature.

## Methods

We included patients with ages between 40-65 years diagnosed with a disease from within the disorders of schizophrenic spectrum: schizophrenia, schizoaffective disorder, delirious disorder, schizophreniform disorder, short psychotic disorder). The I-B group included patients with a history of the disease of maximum 2 years and the II-B group comprised of patients with a history of minimum 10 years of the disease. The main limitations of the patients' selection consisted of the fact that it has not been taken into account the lifestyle (active or sedentary) and that there have been included a small number of subjects of male sex (the sections profile from where they have been selected was preponderant addressed to the persons of female sex), knowing that whether the age, the death risk by CVD seems to be delayed at women, the SCORE diagram showing that it is relatively delayed with 10 years. However, the cardiovascular diseases remain an important cause of death at women, the mortality being with 50% higher in women with age under 55 years compared to men after an acute myocardial infarction. Also, the mortality caused by cerebral vascular accidents is higher in women [12, 13].

## Results and discussion

Tables 1 and 2 show the distribution of groups depending on age and gender, respectively. The mean age is comparable between groups, with no statistically significant differences.

**Table 1.** Distribution of groups by age

Age	I-B (n = 47)	II-B (n = 114)
Average $\pm$ SEM [IC95%]	50.97( $\pm$ 0.96) [49.04 la 52.91]	51.57( $\pm$ 0.63) [50.31 la 52.83]
Median (IQR)	51.00 (11.00)	51.00 (12.00)
Min – Max (Range)	40.00 to 63.00 (23.00)	41.00 to 65.00 (24.00)
Standard deviation (variant)	6.59 (43.49)	6.79 (46.10)
Skewness	0.11	0.16
Kurtosis	-1.19	-1.25
Saphiro-Wilk normality test (p value)	0.0181	< 0.0001

**Table 2.** Distribution of groups by gender

Gender	I-B	II-B
Male – No. (%)	3/47 (6.38)	18/114 (15.78)
Female – No. (%)	44/47 (94.61)	96/114 (84.21)

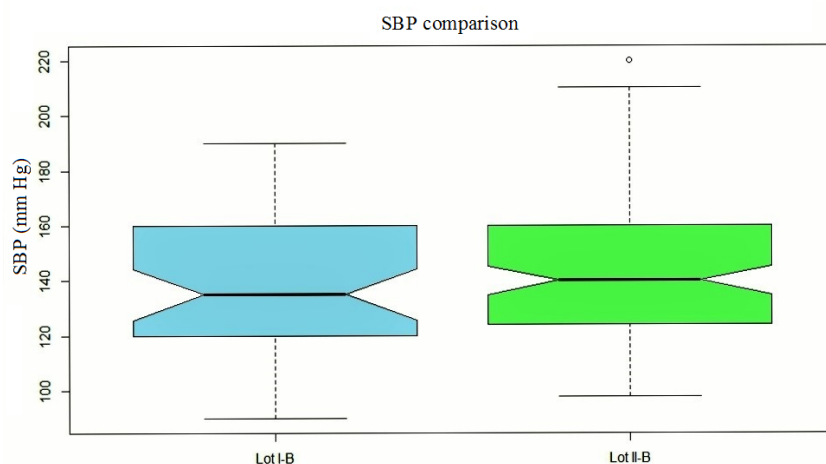
One of the measured variables has been the systolic arterial pressure necessary for calculation of the SCORE index. In the general population the prevalence of the arterial hypertension is of 30-45%. The systolic blood pressure (SBP) seems to be a better predictor for events of cardiovascular nature (cerebral vascular accident, myocardial infarction, sudden death or heart deficiency) than the diastolic blood pressure (DBP) for ages above 50 years. The defined hypertension is defined as a value  $\geq$ 140 for SBP and/or  $\geq$ 90 mm Hg for DBP [14].

Table 3 shows that the values average for SBP is over 140 mm Hg in the group with a prolonged course of the disease. The arterial hypertension prevalence in patients with schizophrenia is 32.8% [15].

**Table 3.** Values of systolic arterial pressure in the two groups

SBP (Systolic Blood Pressure)	I-B (n = 47)	II-B (n = 114)
Average $\pm$ SEM [IC95%]	136.55( $\pm$ 3.73) [129.03 to 144.06]	143.44( $\pm$ 2.48) [138.52 to 148.37]
Median (IQR)	135.00 (40.00)	140.00 (36.00)
Min – Max (Range)	90.00 to 190.00 (100.00)	98.00 to 220.00 (122.00)
Standard deviation (variant)	25.59 (655.03)	26.54 (704.72)
Skewness	0.17	0.47
Kurtosis	-0.69	-0.30
(p value)	0.2752	< 0.0045

To see if there are statistically significant differences between the two groups we used the Welch T parametric test, a bidirectional test starting from the following hypotheses (central tendency of the distributions being appreciated with the help of the arithmetic average): H0 (null hypotheses) –no statistically significant differences between the two groups and Ha (alternative hypotheses) – there are statistically significant differences between the two groups, and the test result ((T = -1.53, df = 88.749, p > 0.05, IC95% which contains 0) do not allow us to reject H0 to a sensibility level  $\alpha = 0.05$  (5%) and we infer that there are no differences with statistical significance between the two groups, to be observed that the two groups of patients are placed from clinical point of view in 2 groups of different risk (under 140 mm those from I-B and over 140 mm those from II-B group), and the p value is however pretty small being possible that the differences to be visible after a longer period of disease evolution (for example after 15 years of evolution to increase the rate, cases of HA at patients with spectrum diseases and implicitly the cardiovascular risk) – Figure 2.



**Figure 2.** Comparison of systolic blood pressure values between the two groups

The second measurable variable has been the total cholesterol because the patients with psychotic disorders have a higher risk of developing some metabolic diseases (diabetes, dyslipidemia, obesity) compared to the general population [16,17,18,19]. The factors which are at the basis of developing

the metabolic syndrome are represented by adverse effects of the psychotropic, sedentary, smoking, unhealthy alimentary customs, reduced preoccupation for a healthy condition, extended stress and genetic predisposition [19,20]. The term of “metabolic syndrome” refers to the association of more factors: obesity, especially central type, arterial hypertension, low HDL-cholesterol, high triglycerides and high blood sugar levels. In patients with disorders of spectrum these factors must be determined as accurate as possible in order to take appropriate measures. Abnormalities of the metabolic profile have been discovered at patients with psychotic disorders, even long before the beginning of the treatment with psychotropic which can mean the fact that the dysmetabolic syndrome represents a feature of the psychiatric disease as it is [20].

Table 4 shows the cholesterol values in the two groups, with higher levels in the group with long course of disorder.

**Table 4.** Comparison of cholesterol levels between the two groups.

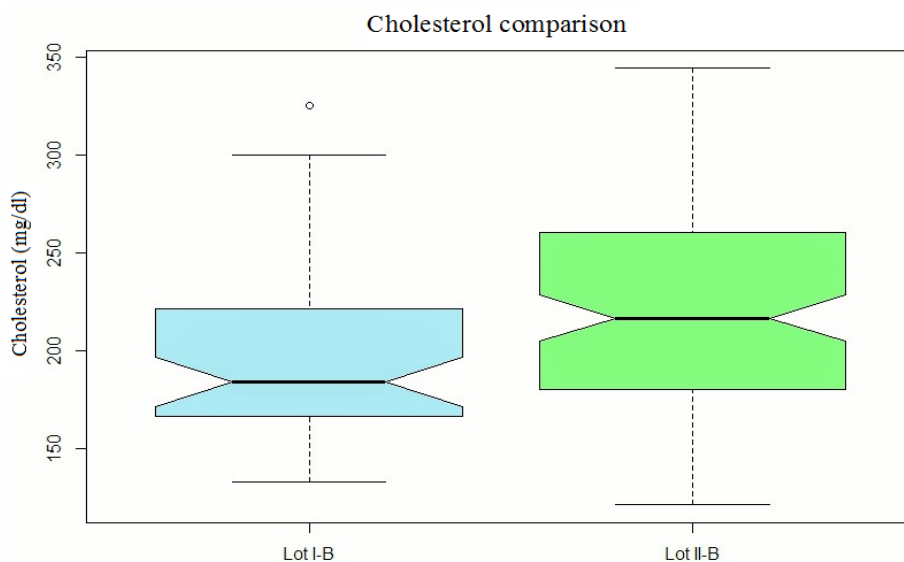
Cholesterol	I-B (n = 47)	II-B (n = 114)
Average $\pm$ SEM [IC95%]	200.31( $\pm$ 7.45) [185.30 to 215.32]	222.28( $\pm$ 4.72) [212.91 to 231.64]
Median (IQR)	184.00 (56.00)	216.50 (80.00)
Min – Max (Range)	133.00 to 325.00 (192.00)	121.00 to 344.00 (223.00)
Standard deviation (variant)	51.12 (2613.26)	50.47 (2547.79)
Skewness	0.96	0.15
Kurtosis	-0.19	-0.72
Saphiro-Wilk normality test (p value)	0.0012	< 0.0382

To investigate if there are differences with statistical significance between the 2 groups we used a Wilcoxon rank sum test (the central tendency of distributions being appreciated with the help of the median), test protected against the errors of type I with the help of a bootstrap procedure for the difference of medians. The test results show a value of p raw of 0,009244 and a p value at the Bootstrap test  $p < 0, 01$  (0,00850),  $\alpha = 0.01$  (1%) and IC95%, meaning that there are statistically significant differences between groups (Figure 3).

In what regards the triglycerides and here the differences between the two groups have been statistically significant registering in the IB groups the following values: average  $\pm$ SEM [IC95%] 126.82( $\pm$ 11.22) [104.22 la 149.23], median (IQR) 102.00 (78.00), standard deviation (variant) 76.97 (5924.92) with p value, Shapiro-Wilk normality test  $< 0.0001$  and for the IIB group: average  $\pm$ SEM [IC95%]-193.18( $\pm$ 15.15) [163.16 la 223.20], median (IQR)- 155.50 (102.00), standard deviation (variant)- 161.78 (26174.22, with p value, Shapiro-Wilk normality test  $< 0.0001$ . Both distributions have been distant of normality (important positive Skewness).

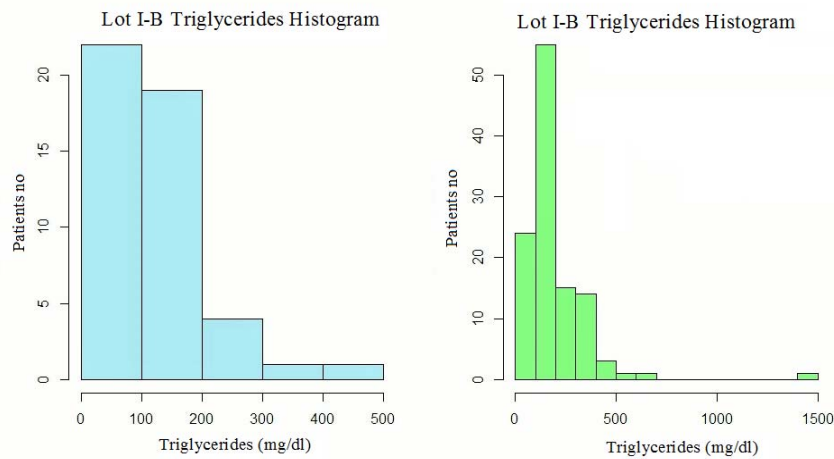
To investigate if there are differences with statistical significance between the 2 groups it is used a Wilcoxon rank sum test (the central tendency of distributions being appreciated with the help of the median), test protected against the errors of type I with the help of a bootstrap procedure for the

difference of medians. The test results show a value of p raw of 0.0001654 and a p value at the Bootstrap test  $p < 0.01$  (0.00010),  $\alpha = 0.01$  (1%) and IC95% which do not contain 0 and infer that there are differences with statistical significance between the 2 groups from the point of view of the series of triglycerides level to be clinically commented (Figure 4).

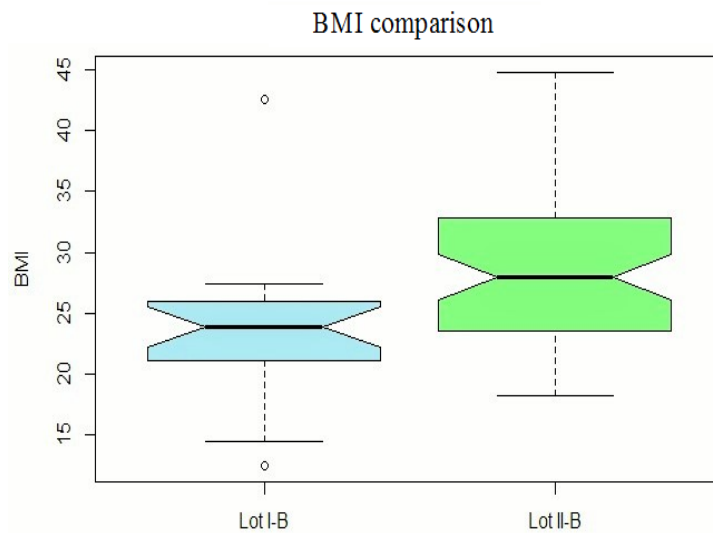


**Figure 3.** Comparison of cholesterol levels between groups

The increased corporal weight is associated with the increase of total mortality and morbidity and by BCV in the general population, mediated partly by the increase of the arterial pressure and of the cholesterol, reducing of the HDL-cholesterol and increase of the probability of appearance of the diabetes mellitus [2], this is the reason it represented an important value to be followed in this study by calculating the index of corporal mass between the two groups of patients. The differences have been statistically significant registering in the IB group the following values: average  $\pm$ SEM [IC95%]-23.62( $\pm$ 1.26) [20.99 la 26.25], median (IQR)- 23.89 (4.92), standard deviation (variant) 5.78 (33.43), with p value, Shapiro-Wilk normality test 0.003159, and for the IIB group: average  $\pm$ SEM [IC95%]-28.74( $\pm$ 0.83) [27.06 la 30.40], median (IQR)- 27.94 (9.23), standard deviation (variant)- 6.56 (43.13), with p value, Shapiro-Wilk normality test 0.03214, and both distributions have been distant from normality (important positive Skewness). After applying the Wilcoxon rank sum test, the results show a value of p raw of 0,0001587 and a p value at the Bootstrap test  $p < 0, 01$  (0,004586),  $\alpha = 0.01$  (1%) and IC95% which do not contain 0 and infer that there are differences with statistical significance, maybe the most evident, between the 2 groups of patients (figure 5). The conclusion is that the extended course generates a significant increase in weight due to the lack of physical activity, most of the patients being medical retired, social isolated or predisposed to poverty and stigmatization.



**Figure 4.** Comparison of triglycerides levels between groups



**Figure 5.** BMI comparison between groups

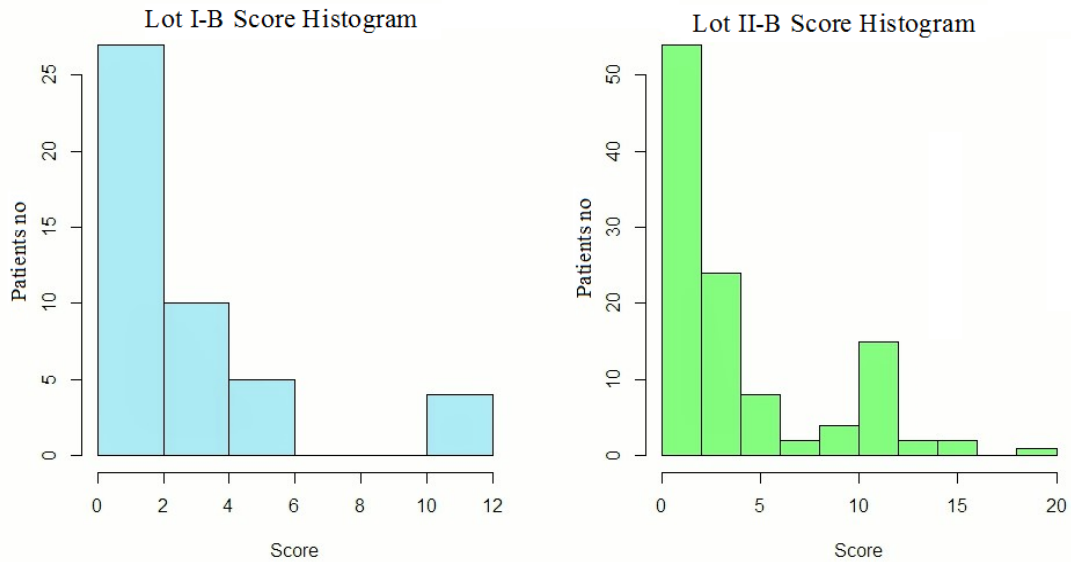
The analysis results for calculation of SCORE index are given in Table 5 and Figure 6.

**Table 5.** SCORE index analysis between groups

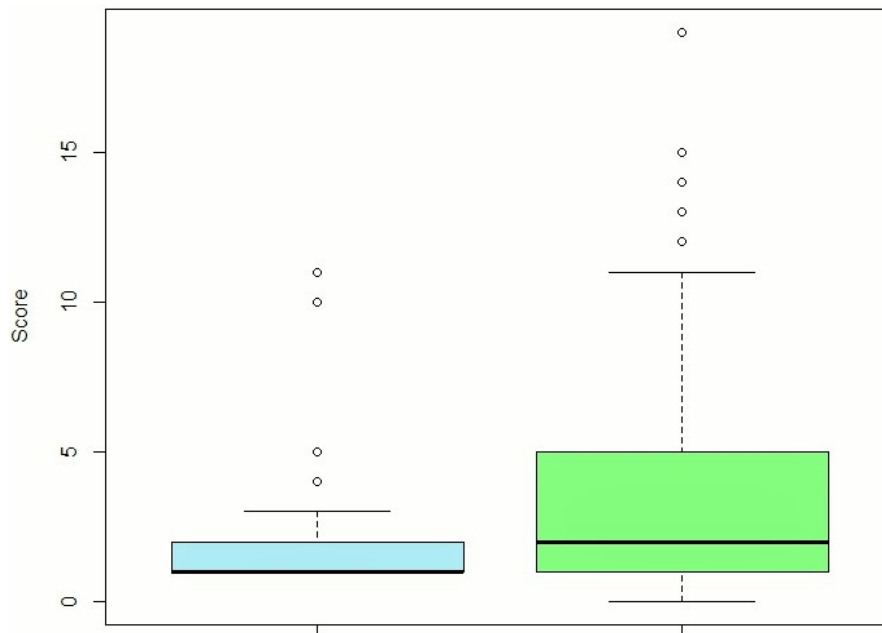
SCORE	I-B (n = 47)	II-B (n = 114)
Average $\pm$ SEM [IC95%]	2.45( $\pm$ 0.39) [1.65 to 3.25]	3.75( $\pm$ 0.38) [3.00 to 4.51]
Median (IQR)	1.00 (1.00)	2.00 (4.00)
Min – Max (Range)	1.00 to 11.00 (10.00)	1.00 to 19.00 (18.00))
Standard deviation (variant)	2.69 (7.27)	4.04 (16.34)
Skewness	2.23	1.48
Kurtosis	4.12	1.38
Saphiro-Wilk normality test (p value)	< 0.0001	< 0.0001

After a statistical analysis (Wilcoxon rank sum test) have been obtained the results: the median difference -1.00, the Wilcoxon sum W 2187,5,  $p < 0,05$  ( $p$  raw 0,1026),  $p$  value Bootstrap 0,392, IC95% determined by bootstrap -2.00 to 0.5, what, at a sensibility level  $\alpha = 0.05$  (5%) leads to the conclusion that there are no differences with statistical significance between the 2 groups from the score point of view, in any of the group the average did not have increased risk value, over 5. It can

be observed (figure 7), however, that the groups are comparable as age, the difference is over one point, that in the second group some patients have presented a very high value of the index, even higher than 15%, which allows us to believe that the extended course of the psychiatric disorder brings an additional risk of death by cardiovascular death in the following 10 years.



**Figure 6.** Comparison of SCORE index between groups



**Figure 7.** SCORE index comparison between the two groups

The general recommendation for a SCORE value  $>5$  consisted of counseling for changing the lifestyle, with reduction of pathological variables (e.g., reduction of the cholesterol value to  $<190$  mg/dl), periodic controls, difficult thing to do for patients with psychotic diseases because they present a low level of the auto-care capacity and of course of the life quality. All these represent a risk factor for relapse or for developing different co-morbidities or aggravation of those already

existing because of the fact that they do not go to the family physician or cardiologist because of a low awareness of the cardiovascular symptoms or erroneous interpretation of them, as well as the fact that despite of the more frequent contacts with specialists from the sanitary system, are less investigated and can be treated with the same attention and consideration as patients with no psychiatric disorder [10, 16].

## **Conclusion**

The research emphasizes a tendency of increasing the factors value which is a risk for developing a CVD, in patients with a course of minimum 10 years of disorder, which imposes a serious and early management of the risk factors.

The Luxemburg declaration from 29<sup>th</sup> June 2005 has defined the necessary characteristics to obtain/maintain the condition of cardiovascular health right in the context of the results of this research and patients with disorders of schizophrenic disorders:

- sustained abstinence in what regards smoking,
- minimum 30 minutes daily of adequate physical activity, of moderate intensity. Patients have to be informed about the physical activity benefits, meaning that almost any increase of the physical activity level has positive effects on health. The additional benefits include a good condition, weight loss and even a better opinion about the person. They have to be encouraged to move, preferable outside, together with friends or family members.
- healthy food, diversified
- SBP under 140mmHg and DBP under 90mmHg
- total cholesterol under 200mg/dl
- BMI<25 kg/m<sup>2</sup> and avoidance of central obesity. Weight loss is recommended at fat persons (BMI ≥ 30 kg/m<sup>2</sup>) and it has to be taken into consideration at overweight persons (BMI ≥ 25 and < 30kg/m<sup>2</sup>). It has to be obtained by alimentary restrictions which suppose corresponding diets, behavioral therapy, change of lifestyle, etc.
- severe control of risk factors in patients with high risk, namely those with installed CVD or diabetes;
- taken into consideration of a cardio-protector drug treatment in patients with high risk, namely at those with installed atherosclerotic CVD and sending patients to a specialist [2, 8, 22].

## References

1. <http://www.ehnheart/>. [Interactiv]
2. Comitetul, E. S. C., and Jeroen Bax. Ghidul european de prevenție a bolilor cardiovasculare în practica clinică (versiunea 2012), 2014, Romanian Journal of Cardiology, Vol. 24.4.
3. Brotons C, Moral I, Soriano N, CUIxart L., Osorio D, Bottaro D., Puig M., Joaniquet X., Marcos A., Casasa A. Impact o Tables for Estimating Cardiovascular Risk. 2014, Rev Esp Cardiol, Vol. 67 (2), 94-100.
4. Conroy R.M., Piorala K., Fitzgerald A.P, Sans S., Menotti, Backer G., Score project group, et al. Estimation of ten-years risk of fatal cardiovascular disease in Europe: the SCORE project. 2003, Eur Heart J, Vol. 24, 987-1003.
5. Mayer JM, Nasrallah HA. Medical illness and schizophrenia. Second edition. Medical illness and schizophrenia. Second edition. London: ISBN 978-1-58562-346-4, 2009, p. 17.
6. Lambert T, Newcomer JW. Are the cardiometabolic complications of schizophrenia still neglected? Barriers to care of. 2009, Med J Aust, Vol. 190 (4 Suppl), 39-42.
7. Campos O.A.M., Nazario N.O., Fialho S.C., Fialho G.L., Oliveeira F., Werner de Castro G.R., Pereira I.A. Assesment of cardiovascular risk in patients with rheumatoid arthritis using the SCORE risk index. 2016, Rev Bras Reumatol, Vol. 56(2), 128-144.
8. Dorobanțu M., Bădilă E., Darabont R., și colab. Studiul SEPHAR- Studiu de Prevalenta a Hipertensiunii Arteriale si evaluare a riscului cardiovascular in Romania, Partea a II-a- Rezultate. 2006, Revista Romana de Cardiologie, Vol. 21.3, 179-189.
9. Dorobanțu M., Bădilă E., Gheorghe S, Darabont R. Total Cardiovascular Risk Estimation in Romania. Data from the SEPHAR Study. 2008, Romanian Journal of Internal Medicine, Vol. 46.1, 29-37.
10. Smith DJ, L. J. Schizophrenia is associated with excess multiple physical healt comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. 2013, BMJ Open 3.
11. Kurdyak P, V. S. High mortality and low access to care following incident acute myocardial infarction in individuals with schizophrenia. 2012, Schizophrenia Research, Vol. 142, pg. 52-57.
12. Vaccarino V, Krumholz H.M, Yarzebsk J, et al. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. 2001, Ann Intern Med, Vol. 134, pg. 173-181.
13. Mozaffarian D, Benjamin E.J., Go A.S., American Heart Association Statistics Committee and Stroke Statistics Subcommittee, et al. Heart disease and stroke statistics - 2015 update: a report from the American Heart Association. 2015, Circulation, Vol. 13129-322.
14. Filipovsky J, Widimsky Jr. J., Spinar J. Summary of 2013 ESH/ESC Guidelines for the management of arterial hypertension/ Czech Society of Cardiology. 2014, Coe et Vasa, Vol. 56, 494-518.

15. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: Data from the CATIE schizophrenia trial sample at baseline. 2006, *Schizophrenia Research*, Vol. 86, 15-22.
16. Vancampfort D., Wampers M., Mitchel A.J, Correl C.U., De Herdt A., Probst M., et al. A meta-Analysis of cardio-metabolic abnormalities in drug naive, first-episode and multi-episode patients with schizophrenia versus general population controls. 2013, *World Psychiatry*, Vol. 12, 240-250.
17. Osby U., Olsson E., Edman G., Hildin A., Eriksson S.V., Ostenson C.G. Psychotic disorder is an independent risk factor for increased fasting glucose and waist circumference. 2014, *Nordic J Psychiatry*, Vol. 68, 251-258.
18. Osborn D.P., Nazareth I., King M.B. Risk for coronary disease in people with severe mental illness: cross-sectional study in primary care. 2008, *Br. J. Psychiatry*, Vol. 188, 271-277.
19. Bartoli F., Crocamo C., Caslini M., Clerici M. Schizoaffective disorder and metabolic syndrome: A meta-analytic comparison with schizophrenia and other non-affective psychoses. 2015, *Journal of Psychiatric Research*, Vol. 66-67, 127-134.
20. Darcin A.E., Cavus S. Y., Dilbaz N., Kaya H., Dogan E. Metabolic syndrome in drug-naive and drug-free patients with schizophrenia and their siblings. 2015, *Schizophrenia Research*, Vol. 166, 201-206.
21. Bo S., Kongerslev M., Dimaggio C, Lysaker P.H, Abu-Akel A. Metacognition and general functioning in patient with schizophrenia and a history of criminal behavior. 2014, *Psychiatry Research*, Vol. 225, 247-253.
22. Millen B., Wolongevicz, Nonas C., Lichtenstein A. 2013 American Heart Association/American College of Cardiology/The Obesity Society Guideline for the Management of Overweight and obesity in Adults Implications and New Opportunities for Registered Dietitian Nutritionists. 2014, *Journal of the Academy of Nutrition and Dietetics*, Vol. 114, 1730-1735.

## COPYCAT SUICIDES IN BULGARIA - THE ROLE OF THE MEDIA

Plamen Atanasov<sup>1</sup>, Vladimir Nakov<sup>2\*</sup>, Jordan Ganev<sup>3</sup>, Tony Donchev<sup>3</sup>

<sup>1</sup>Sofia University St. Kliment Ohridski, Bulgaria

<sup>2</sup>National Centre for Public Health and Analyses, Sofia, Bulgaria

<sup>3</sup>Military Medical Academy, Sofia, Bulgaria

### **Abstract**

*Introduction: Suicide as a problem is a subject of study of many disciplines. The media are an important source of the formation of views and beliefs. The role of the media in suicidal behavior has been discussed for many years. In our literature, this problem is not considered. The aim of our study was to trace the relationship between media coverage of completed suicides in Bulgaria.*

*Methods: There are standard forms "death notification" and "card for suicidal action" of the Ministry of Health. The information is collected by the regional health inspections and summarized by the National Center for Public Health and Analyses. We have undertaken an overview of media coverage of the completed suicides in 2013 and 2016.*

*Results: It was found a significant increase in death by suicide in the months following the massive coverage of the first self-immolations in Bulgaria. There is a second peak after the coverage of self-immolations in the summer of 2013.*

*Conclusion: Journalists need to be systematically taught how to present this special sensitivity information about suicide.*

**Keywords:** *suicide, media, prevention.*

### **Introduction**

It has been a long known fact that committed attempts and completed suicides can lead to a brief series of self-destructive actions in impressionable people who know the committed suicide or received the information about it from the media.

Imitative suicides and attempted suicides are the result of suggestive effect of people from the immediate environment of suicidal people [1] - from the same school, prison, hospital wing, military unit, office or as a result of detailed reporting case in the press [2-13].

Similar attempts or suicide are called "cluster" and are common in adolescents aged 15-19. The share of suicide cluster in adolescence is between 1 and 13% [2].

Mechanism of imitation:

The term "Werther effect" to describe this phenomenon occurs after the publication of the Goethe's book "The sorrows of young Werther" in 1774. The book describes the history of the young

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\* Correspondence: *Vladimir Venkov Nakov MD, PhD. 1431 Sofia, Acad. Iv. Geshov blvd 15, fl. 9, office 20. Tel.: 359 2 954 97 69; e-mail: vnakov@gmail.com.*

Werther who shoots himself as his love was rejected [11]. Many young people did the same which forced the authorities in Italy, Leipzig, Copenhagen and other cities to prohibit this book due to the fear of dangerous wave of suicidal acts.

A key mechanism of cluster suicides is the "identification" [1, 12]. Impressionable people who find their situation hopeless and who have a sense of helplessness or are in a state of crisis and/or depression may find many similarities between themselves and the people who had sacrificed their life despite the presence of constructive alternatives.

They can easily be influenced to attempt suicide, especially if the media invariably describe suicide as impulsive result of life's stressful situations or as spectacular, romantic act and do not represent an adequate analysis of mental illness and psychosocial problems that are based on what happened.

### **WHO Guidelines for the provision of information about suicides in the media:**

Evidence-based studies reporting that reduction of cluster suicide can be achieved with properly compiled information, do not exist. On the other hand, there is a quite obvious connection between sensational and irresponsible presented messages and their role to accelerate or induce suicidal actions. The responsible attitude of the media to provide information on suicide actions may counteract the cluster suicides [12, 14].

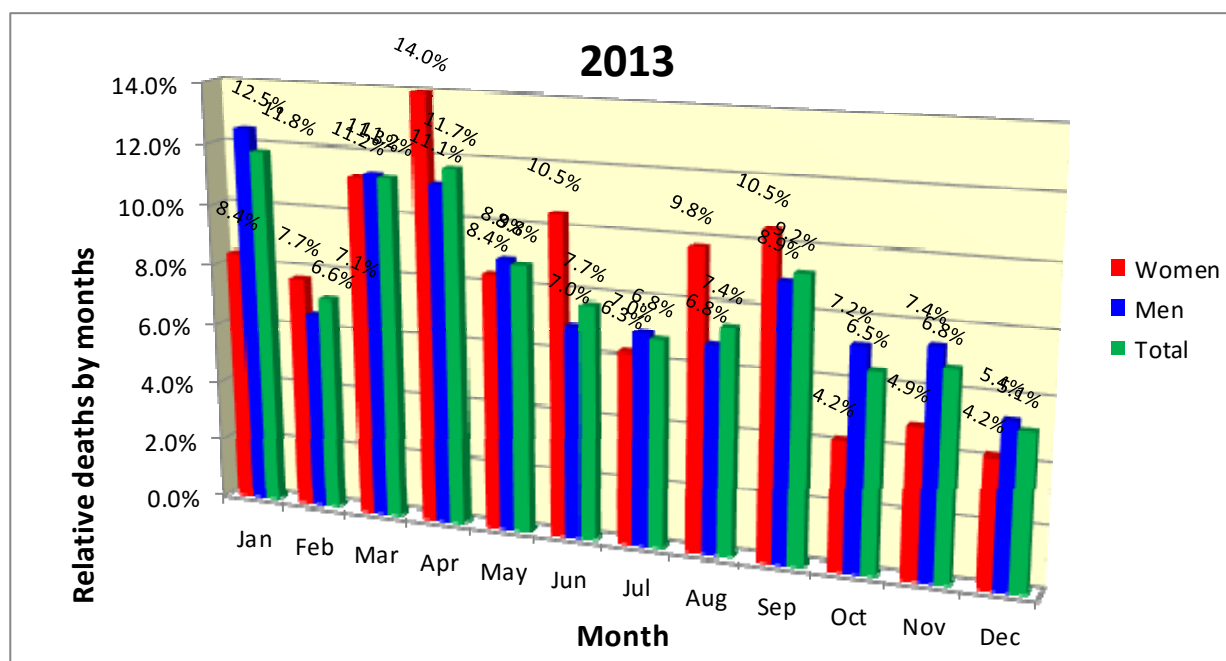
WHO has developed detailed instructions for exporting reports of suicides in the mass media [15]. The basic rule is to not search for the sensation at presentation of news as it adds an extra "heroism" and to present the act in the desired plane. There should not be any photographic materials, detailed description of the method of suicide or any mysterious, romantic, inexplicable presentation of it. It is necessary to expose the psychosocial conditions and their role in making decisions about death. The possible role of mental diseases /most often depression/ but also alcohol and/or other psychoactive substances should be clarified. It should be emphasized that these conditions are completely curable in modern conditions. It is important to set out to this information the possible places to summon help. Positive examples for resolution of serious conflicts can be presented without being associated with suicidal actions. Furthermore, the possible serious personal consequences can be described as a result of a suicide attempt - severe brain damage or paralysis. It is important to make recommendations for a possible situation management and to prevent further suicide acts. The most important thing is to avoid the image formation of a martyr, mystery or glorification of suicide. It is estimated that the number of imitative suicides reduced if the information is presented as an alternative to a suicide which is accompanied by well considered and presented data on overall suicidal picture, possible means of prevention and/or treatment. Mandatory part of the data is the information on where to get help /the exact name and institution, address, telephone number.

The first evidence of imitative suicides in Bulgaria is from 1927 when Ilya Yanulov described cases of imitation of the place and the method of suicide as a result of media coverage [2].

Self-immolation /pouring on flammable liquid and setting oneself on fire/ is not typical for Bulgaria. It is unreliable and extremely painful way to commit suicide. Fear of burning is a well-known fact - during fire in tall buildings people prefer to jump and die falling on the ground and not in flames. This method is used rarely and not before 1989 according to the data of T. Tashev but the authoritative information is not exported about the cases. M. Baltov registered 9 cases of self-immolation in Plovdiv region for 10-year period [1].

The conducted analysis of media coverage showed incompliance with the requirements under item 5 (The suicidal behavior must not be allowed to be recognized as an understandable response to social or cultural issues or degradation of personality). In this section, it is mostly manifested. Also, obvious and significant breach of paragraphs 1, 2 and 4 of the guidelines of the WHO were registered. The most complete is the coverage of requirements on cautious comments, suggesting that the social significance of the event is more exploited leading to heroization and is also a precondition for "Werther syndrome" and for subsequent attempts.

The compliance with the basic ethical requirements for media reflected news in the area of suicidal manifestation seriously concerns the media responsibility to the public interest and existential human rights. There is no reason to consider it in the light of infringement of awareness, the more that the sample of material reveals gaps also in the reliability of the information source (item 2).



The graph shows the increase in death by suicide in 2013 after detailed media coverage in February and July.

The results showed intention of the media to a socially responsible position, combined with the rejection of trivial problems. The methodical analysis shows that the omissions differ significantly from public acceptability and content of the event, the cause of which is the lack of clear definitions on unauthorized presenting of not only suicidal events but also violence in the media. The establishment of such rules is the task of an interdisciplinary work between specialists from different fields - psychology, sociology, journalism and others.

Three years later, our observation showed that the media have not only forgotten what happened, but even protest against the monitoring report of the national institution caring for the hygiene of the media space - the Council for Electronic Media [18].

The suicide attempt of a famous Bulgarian gymnast was reflected by the media extremely in details, on a daily basis and at any time in printed journals and newspapers, radio and television broadcasts. As a result, only in the capital city of Sofia three deadly jumps off high buildings were registered for two weeks following the case.

The method "jumping from a height" holds the fourth preference position in suicide attempts and second as a share in completed suicides. Data analysis after the calendar year will allow claiming with certainty whether there is an effect on the entire country.

The scientific examination of the issue of suicides has nothing to do with their sensational media coverage. Imitation plays an essential role in the particularly vulnerable groups of individuals. Therefore, a necessary part of prevention efforts should be directed to training of media professionals.

## References

1. Наков, В, Дончев, Т. Самоубийствата в България 2009-2013, София, 2015, 76 [Nakov, V, Donchev, T. Suicides in Bulgaria 2009-2013, Sofia 2015, 76, in Bulgarian]
2. Янулов, И. Морална статистика, София, 1927, 4, 127-130 [Yanulov, I. Moral statistics, Sofia 1927, 4, 127-130, in Bulgarian]
3. Hazell P. Adolescent suicide clusters: Evidence, mechanisms and prevention. Austr. and New Zealand J. of Psychiatry. 1993; 27:653-665.
4. Gould M.S. Teenage suicide clusters. JAMA 1990b; 263:2051-2052.
5. Cox B., Skegg K. Contagious suicide in prisons and police cells. J. of Epidemiol, and Community Health. 1993; 47:69-72.
6. Rissmiller D.J., Rissmiller F. Inpatient suicide epidemics and suggestions for prevention. Hospital and community psychiatry. Hosp. Community Psychiatry. 1990: 41:922-924.
7. Taiminen T.J., Helenius H. Suicide clustering in a psychiatric hospital with a history of a suicide epidemic: A quantitative study. Am. J. of Psychiatry. 1994; 151:1087-1088.

8. Rubinstein D.H. Epidemic suicide among Micronesian adolescents. *Social Science and Medicine*. 1983; 17:657-665.
9. Hankoff L.D. An epidemic of attempted suicide. *Comprehensive Psychiatry*. 1961; 2:294-298.
10. Etzersdorfer E., Sonneck G., Nagel-Kuess S. Newspaper reports and suicide. *N. Eng. J. Med.* 1992; 327:502-503.
11. Marzuk P.M, Tardiff K., Hirsch C.S. et al. Increase in suicide by asphyxiation in New York City after the publication of *Final Exit*. *N. Engl. J. Med.* 1993; 329(20): 1508-10.
12. Philips DP. Carstensen LL. Clustering of teenage suicides after television news stories about suicide. *N. Eng. J. Med.* 1986; 315:685-689.
13. Schmidtke A., Hafuer H. The Werther effect after television films: New evidence for an old hypothesis. *Psychological Medicine* 1988; 18:665-676.
14. Schmidtke A., Sclialler S The role of mass media in suicide prevention. In: K. Hawton and K. van Heenngen (eds). *The International Handbook of Suicide and Attempted Suicide*. New York. Wiley. 2000:675-697.
15. Stack S The effect of the media on suicide: evidence from Japan, 1955-1985. *Suicide Life Threat.* Be haw 1996; 26(2): 132-142.
16. Bennan A., Johes D.A.. O 'Carroll P. The aftermath of Kurt Cobam's suicide. In. De Leo D., Schmidtke A., Diekstra R.F.W. *Suicide Prevention: a Holistic Approach*. 1997:139-143
17. World Health Organization, Geneva 2000. *Preventing suicide: A resource for media professionals*. Department of Mental Health, Social Change and Mental Health.
18. <http://www.cem.bg/controlbg/858>.

## PATIENT-RELATED RISK FACTORS OF BEING RESTRAINED IN ACUTE PSYCHIATRIC HOSPITAL IN ROMANIA

Alex Mihai<sup>1,3</sup>, Maria Crainic<sup>1</sup>, Madalina Mocan<sup>1</sup>, Ina Alexiev<sup>1</sup>,  
Alexandra-Paula Sărmășan<sup>2</sup>, Adriana Mihai<sup>2,3\*</sup>

<sup>1</sup>University of Medicine and Pharmacy „Iuliu Hațieganu”, Cluj-Napoca, Romania

<sup>2</sup>University of Medicine and Pharmacy, Targu Mures, Romania

<sup>3</sup>Institute of Psychotherapy and Personal Development (IPPD), Targu Mures, Romania

### **Abstract**

*Introduction: Seclusion and restraining in psychiatry wards is a common practice when patients tend to harm themselves, other patients or medical staff. Seclusion and restraining decision making is a complex process based on violence potential, patient's antecedents, staff experience and hospital internal regulations. The aim of this study is to evaluate the characteristics of patients restrained in acute psychiatric hospital.*

*Methods: This 2 years retrospective study conducted on a total of 1000 patients randomly selected, admitted in an acute Psychiatric Hospital. The risk factors related with patients' characteristics were evaluated.*

*Results: 10% of total patients admitted were restrained during the admission. No significant differences in restraints practice related with group diagnosis, except patients with alcohol addiction where is statistically significant ( $p < 0.05$ ). Out of the patients with recurrent depressive disorder younger patients were more frequently restrained. No significant differences in restraint practice related with gender or rural/urban origin was found. In 2014 comparing with 2013, the number of restraints in emergency admission increased with 16% but not statistically significant ( $p = 0.08$ ). Significantly more males are admitted in emergency than females ( $p = 0.01$ ). Males (66%) were far more frequently restrained than females (34%) when have been admitted through the emergency room. The average number of restraints per patient has increased from 1.6 times in 2013 to 1.9 times and the duration of restraining has increased from 1.02 hours/patient in 2013 to 1.51 hours/patient in 2014, from 4 hours maximum duration legally accepted.*

*Conclusion: The risk factors for being restrained in acute psychiatric hospital found in this study were: admission for emergency situation, male gender, agitation, hetero-aggressive behavior, diagnosis of alcohol addiction and in those with affective disorder younger age.*

**Keywords:** *coercive measure, restraining methods, mechanical restrains, violence, emergency, acute psychiatric hospital.*

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\* Correspondence: *Adriana Mihai*, IPPD Targu Mures, Romania. Tel.: +40365882188; e-mail: [ippdms@yahoo.com](mailto:ippdms@yahoo.com).

## **Introduction**

The aggressive behavior as result of psychiatric disorders, when the person put in danger other persons or his/her own self, can be treated compulsory in a psychiatric hospitalized medium. Aggression behavior can be observed in a number of diagnoses psychiatric or non-psychiatric. Some psychiatric disorders such as psychosis, melancholia, neurosis associated with personality disorders, substance use are more predisposed to violence than others [1,2].

In situation with aggressive behavior, which not responding to de-escalation process, constraining methods need to be used to prevent potential harm. Nurses express their frustration when having to confront with aggressive behavior, and not having a proper training in dealing with it [3]. Training staff to manage violent behaviors and restraining methods is mandatory in these units. Even when nurses are trained in techniques of restraining ethical issues of deciding if a patient actually needs to be constraint can have a negative effect on nursing personnel [4].

Training nursing personnel in restraining techniques started from early 1985 in U.K. as a response to defend itself or to prevent injuries to other patients. Techniques such as three persons restraint team, prone position, when the patient is facing to the floor, and breakaway techniques should be mandatory for any nurse training course [5].

Restraining or seclusion decision making is a complex process, combining cues related with patient, personnel and organization. The most important elements analyzed are violence potential, patient's antecedents, staff experience and hospital internal regulations. Patient behavior is assessed by the nursing personnel based on speech, content of thinking, and mood. If the patient threatens to be aggressive to him/her-self, other patients or staff members, restraining or seclusion methods are used as an alternative to a worst outcome. Organization rules and practices are different from institution to institution, the outcome of seclusion and restraining decision making being different. The restraining methods and seclusion are thought to be used only when there is an actual risk of injury. The low personnel, number of beds and high number of patients can lead to using these techniques in the hopes of keeping the ward a calm environment [4].

The aim of this study is to evaluate the characteristics of patients restrained in acute psychiatric hospital.

## **Methods**

Out of 3344 acute patients that were admitted to Psychiatric Ward of County Clinical Hospital during 2013 (1747) and 2014 (1597), 1000 were randomly selected and represent patients included in analysis. The sample group was divided in group 1 of patients which were restrained during the admission period and group 2 – control group that includes all others patients from selected sample, which have not been restrained during the admission period. The information used was screened

from patients' medical files and the register of restraints from the closed psychiatric ward. All the patients were admitted due to mental disorders. The acute hospital admission could be done on emergency situation or on regular bases by a scheduled admission.

Demographic variables like gender, age, and environment were taken into account and correlated with the following medical variables: final diagnosis, medication, symptoms that are considered risk factors for restraining and the type of restraining used.

The programs used for data analysis was IBM SPSS 20 version.

## Results and discussions

Out of the total 1000 patients included, 569 were females, representing 56.9% of the sample group, with a significant higher prevalence than males,  $p < 0.001$ . The male age range was from 15 to 85 years old and the female one from 16 to 83 years. The average age was 50.34 years.

Patients were also classified based on the type of area they lived in, 54.7% ( $n = 547$ ) were from an urban area, significantly more from this area  $p < 0.001$  than rural area, but with no significant difference between genders (54.1% female and 55.5% male from urban area) A higher frequency of female gender in admitted patients was noticed in both rural and urban area, statistically significant  $p < 0.001$  (Table 1).

**Table 1.** Repartition based on gender and area of origin

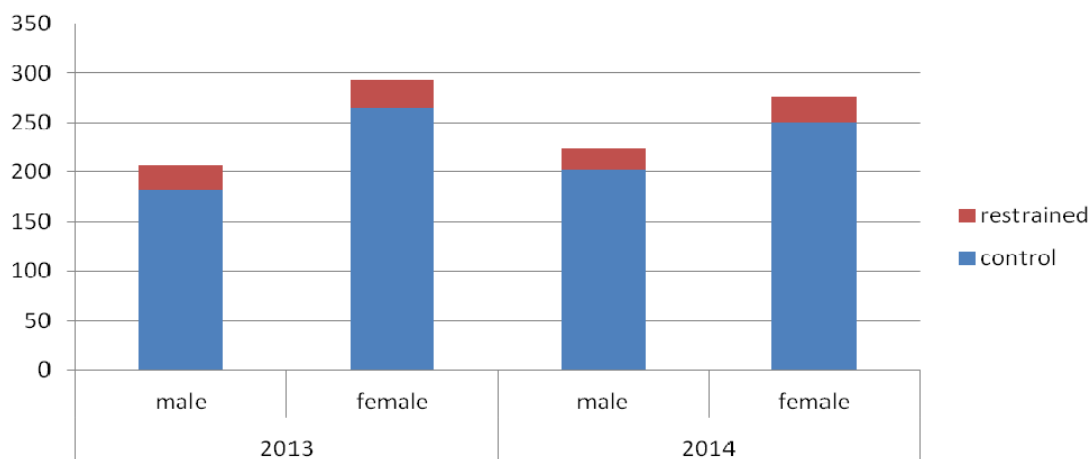
Sample group characteristics	Rural	Urban	Total
Male	192	239	431
Female	261	308	569
Total	453	547	1000

Through the emergency room were admitted 203 patients, representing 20.3% of the total number of patients. 31 of these patients were in need of restraining, meaning 15.27% of the urgent cases. The risk of being restrained is significantly higher for those admitted in emergency  $p = 0.02$ . Out of the total number of 1000 cases, 100 (10%) were restrained. Significantly more male are admitted in emergency than female ( $p = 0.01$ ). Males (66%) had significant higher risk to be restrained while admitted through the emergency room (Table 2).

**Table 2.** Repartition based on hospitalization type and whether or not they were restrained

Hospitalization type	Patients not restrained	Restrained Patients	Total patients
Emergency Room	172	31 (15.3%)	203
Regular Admission	728	69 (8.7%)	797
Total	900	100 (10%)	1000

No significant differences in restraints practice related with gender or rural/urban origin. In 2014 comparing with 2013, the number of restraints in emergency admission increased with 16% but not statistically significant ( $p=0.08$ ) – Figure 1.



**Figure 1.** Gender distribution in restrained and control group in 2013 and 2014

Patients were also grouped based on their final diagnosis and the most frequent mental illness for both sexes was Recurrent Affective Depressive Disorder 36.5% (365), followed by Schizophrenia with 19.9% (199) of the sample group. Personality Disorder was the third most common cause 8.8%, then Alcohol-Related Disorder 8.7%, Anxiety Disorder 6.5%. The least frequent ones were Bipolar Disorder 2.2% and Delusional disorder 1.8% (Table 3).

**Table 3.** Diagnoses distribution of patients restrained and in control group

	Recurrent Depressive Disorder	Bipolar Disorder	Anxiety	Schizo-affective disorder	Schizophrenia	Delusional Disorder	Alcohol addiction	Personality Disorder	Others	Total patients
Group 1 Restrained Patients	39(39.00%)	3(3.00%)	6(6.00%)	3(3.00%)	11(11.00%)	2(2.00%)	14(14.00%)	7(7.00%)	16(16.00%)	100
Group 2 control	326(36.22%)	19(2.11%)	59(6.55%)	49(5.44%)	134(14.88%)	16(1.77%)	73(8.1%)	81(9%)	143(15.9%)	900
p	p=0.58 NS	p=0.56 NS	p= 0.83 NS	p=0.29 NS	p=0.29 NS	p=0.87 NS	<b>p&lt;0.05</b>	p=0.50 NS	p=0.99 NS	

Recurrent Affective Depressive Disorder was the most often established diagnosis for both the male and female group, presenting a positive Odds Ratio (male OR=9.71; female OR=7.69) for restraining and a statistically significant association between diagnosis and risk of being restrained ( $p=0.001$  male and female group). The same is true for Schizophrenia in both gender groups (male OR=6.11,  $P=0.001$ ; female OR=4.84,  $P=0.006$ ), while for females the positive Odds Ratio and significant association is available for Acute Psychotic Disorder (OR=5.12,  $P=0.007$ ), too. There is a notable difference in prevalence of female patients suffering from Recurrent Depressive Disorder, compared to male patients (25.41%).

Regarding the area of origin of the patients, there is a slightly higher percentage of patients suffering of Recurrent Depressive Disorder from urban areas (36.99%), than does from rural areas (35.76%).

This is also the case when the diagnosis is Schizophrenia: urban area 21.97%, rural 17.43%.

There are no statistical differences in substance used as treatment for patients with restraining comparing with control group, there are only slightly increase doses in sedatives and neuroleptics. Out of the restrained patients younger usually suffering of schizoid disorder were more frequent, although comparing to the larger group of the total patients admitted no significant differences were found.

The patients which had mechanical restrained intervention fulfill all legal criteria need it for this procedure [6]. The main symptom of these patients was psychomotor agitation in 91% of them and/or hetero-aggressive behavior in 82%. The impulsivity, agitation and aggressive behavior are frequently associated [7]. There is no statistical difference between genders.

The method of coercion which use mechanical restrains could be devised in five categories depending on level of violence: total restraining of all four members, partial restraining of both arms, partial restraining of both legs, one leg restrain and one arm restrain. In our study at 82% of patients both arms were restrained, at 11% both legs, 3% one leg, 2% one arm and 2% all four members. The level of restraining depends on severity of symptoms and reaction to medication administrate. The mechanical restrain are use only until the drugs as sedatives, neuroleptics, hypnotics have effect. This method are used only when the de-escalation measures were unsuccessful and patients are in danger for themselves or put in danger staff or other persons [8].

The patient have to be evaluated by a specialist in psychiatry which decides if this measure needs to be used, which drug has to be administrated and if the patient should remain under the permanent or frequent (every 5 minutes) evaluation of a medical nurse. Every 30 minutes the need of continuing the mechanical restrain is evaluated. In our study the average duration of restrain was 1.02 hours/patient in 2013 to 1.51 hours/patient in 2014. The maximum duration legally accepted is 4 hours [6].

The same patient could be restrained several times in the same admission depending on his/her psychic states. The average number of restraints per patient has increased from 1.6 times in 2013 to 1.9 times in 2014. There are different factors which are not related with patients' characteristics which could influence this decision; for example: the workload, number of bed/nurse, lack of medical staff, number of agitated patients in same time, lack of training of nursing staff, department characteristics – lack of isolation room, etc.

## **Conclusion**

The risk factors for being restrained in acute psychiatric hospital found in this study were: admission for emergency situation, male gender, agitation, hetero-aggressive behavior, diagnosis of alcohol addiction and in affective disorder at a younger age.

## References

1. Hecser L., Ardelean M., Jung H. Psihiatria și medicina legala: elemente corelative, Editura University Press Tg. Mures, 2008.
2. Rădulescu M.S.- Sociologia violenței (intra)familiale. Victime și agresori în familie, Editura Lumina Lex, București, 2001.
3. Ford R. Interpersonal challenges as a constraint on care: The experience of nurses' care of patients who use illicit drugs. *Contemporary Nurse* (2011) 37(2): 241–252.
4. Laiho T., Kattainen E., Åstedt-Kurki P., Putkonen H., Lindberg N., Kylma J- Clinical decision making involved in secluding and restraining an adult psychiatric patient: an integrative literature review. *Journal of Psychiatric and Mental Health Nursing*, 2013, 20, 830–839.
5. Steve Wright, Jane Sayer, Ann-Marie Parr, Richard Gray, Dylan Southern, Kevin Gourney,- Breakaway and physical restraint techniques in acute psychiatric nursing: Results from a national survey of training and practice. *The Journal of Forensic Psychiatry & Psychology*, June 2005; 16(2): 380 – 398
6. Legea sănătății mintale și a protecției persoanelor cu tulburări psihice nr. 487, 11 iulie 2002, republicata în 9septembrie 2012, [www.dreptonline.ro/legislatie/legea\\_sanatatii\\_mintale.php](http://www.dreptonline.ro/legislatie/legea_sanatatii_mintale.php)
7. Albert-Lőrincz E. Promovarea sănătății mintale și supervizarea: condiții de bază ale profesionalizării muncii asistenților social în relația lor cu beneficiarii, *Revista de Asistență Socială - Social Work Review*, 2010, 2: 65-74.
8. Mihai A. Agresivitatea, o abordare bio-psiho-sociala. Editura Risoprint, Tg Mures, 2013.

## MENTAL HEALTH SERVICES: WHY PEOPLE ACCESS THEM... OR DON'T?

Andreea Raluca Tirintica\*, Geanina Andreea Ilinoiu, Jozsej Andras Szavuj, Adriana Mihai  
University of Medicine and Pharmacy Targu Mures, Romania

### **Abstract**

*1 in 4 adults (450 million people worldwide) experiences mental illness in a given year and approximately 60% of people with a mental illness received no mental health care. Despite effective treatments, there are long delays (sometimes even decades) between the first appearance of symptoms and the moment when people get help. As Hippocrates said once, it seems that even in our days "Healing is a matter of opportunity." So we should ask ourselves: why people access mental health services... and why they don't? Do we really understand what's happening between the first psychiatric symptoms and the moment when people get treated? Are there any needs in the present mental health system which can be influenced in order to improve the access to care? Making a review of the factors influencing patients' access to mental health services could create a pathway for a new research in this direction, as there are many reasons that could influence people in seeking help for mental problems and a larger systematized study would be useful in this regard.*

**Keywords:** access, factors, mental health, services.

### **Introduction**

In ancient times, mentally ill people were isolated, chained, exposed to lack of sleep or food or cold, to harsh treatments, to exorcism and stigma. They were treated like animals and many experiments were done on them. (Shorter, 1997) In time, science developed and modern psychiatry was born: new treatments and a larger view of mental illness appeared.

We are living in a world which is continuously changing and mental health is not anymore defined as the absence of disease, but as the capacity of the individual to achieve his own potential in life and in society (WHO, 2014).

So times had changed: but so did the mentality of people? Are mental health systems still suffering from the way the mental illnesses were dealt with in the past? In a time when an important variety of treatments is developing, are we really moving forward?

Statistics show that 1 in 4 adults (450 million people worldwide) experiences mental illness in a given year (WHO, 2001), but approximately 60% of people with a mental illness received no

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\* Correspondence: *Andreea Raluca Tirintica*, The University of Medicine and Pharmacy Targu Mures, Department of Psychiatry, Gheorghe Marinescu Street, No. 38, 540138.  
Tel. +40722406741; Fax: +40265311840; e-mail: raluca Tirintica@yahoo.com.

mental health care (Rockville, 2012) because of multiple factors. Despite effective treatments, there are long delays (sometimes even decades) between the first appearance of symptoms and the moment when people get help. (NHA, 2005) As Hippocrates said once, it seems that even in our days, “Healing is a matter of time, but it is also sometimes a matter of opportunity.”

The consequences of this fact are really important: decreased quality of life and a higher risk of worse outcome, unemployment, an increased cost of different services involved (ambulances, hospitalization, police...), stigma and exclusion etc.

Isolated studies were done in different parts of the world and a revision of those studies would be useful to create a premise for a systematized and larger research, in order to find the needs in the present mental health system and to improve it. The aim of our review is to check the most important factors influencing patients’ access to mental health services, studied in the last decade.

## Material and methods

MEDLINE and PubMed databases were used to search relevant articles published in different journals in the last decade (from 2004 to 2014). The issue of access to mental health care, which was always an important question, is not clarified even in our days. Yet studies were realized from different points of view, and the use of mental health services, the pathway to care, the factors influencing the access to psychiatric treatments and the barriers to mental health care, both in patients and health professionals’ opinion, were evaluated in studies realized in different parts of the world. The search was conducted using the following terms: factors, access, mental health services.



**Figure 1.** Studies on access to mental health services: Chile (Saldivia, 2004), France (Younes, 2005; Kovess-Masfety, 2007; Townsend, 2012), Eastern Europe (Gater, 2005), US (Bradford, 2008; Keyes, 2012), United Kingdom (Thomas, 2009), India (Jain, 2012; Reddy, 2013), Australia (Rossetto, 2014)

### **Mental health service utilization in Chile**

In 1992-1999, in 4 of the 13 regions in Chile, a representative sample of 2,987 participants older than 15 years (who were considered adults, according to health service system in Chile) were questioned about mental health service utilization, with a response rate of 90.3%. CIDI (The Health Problems Questionnaire) was used to conduct the interviews and the diagnoses were based on DSM-III, using a rating of the severity of mental health problem. The participants were asked about using any health care service, public or private, formal or informal, and about barriers to care, and a list of reasons were provided to choose from it. Data analyses were performed using Chi-square tests and logistic regression, in an attempt to find the barriers to mental health care in Chile, 20 years ago. (Saldivia, 2004)

### **Pathway to mental health care in Europe**

In Europe, a study published in 2005 tried to reveal the way people seek help for mental disorders in 8 centers from 6 countries in Eastern Europe (Serbia, Romania, Bulgaria, Macedonia, Albania and Croatia). Samples of 50 patients diagnosed using ICD-10 criteria from each country were interviewed. Encounter Form (developed by World Health Organization in 1999) was applied and data were analyzed using x2-test. (Gater, 2005)

### **Collaboration general practitioners – mental health providers in France**

An unitary conclusion in the last years in EU countries regarding the difficulties in health care systems was the value of general practitioners in our health care systems and implicitly, in mental health care. The GPs (General Practitioners) in the South Yvelines area – France (492 GPs) completed a satisfaction questionnaire about their practice with PMHP (patients “for whom a mental health problem was the main current problem”) and about their collaboration with MHPro (mental health professionals), with a response rate of 36.6% (180). The GPs included in the study 1519 PMHP (15% of their patients). The premise of the study was that some patients with mental illness seek help to GPs, but in some cases their problem is not recognized or is not adequately treated. The first part of the questionnaire evaluates the GPs’ opinion on their practice in mental health field and with PMHP and their relationship with MHPro. After that, the GPs completed questionnaires for each PMHP included in the study, evaluating demographics, CIM-10 diagnoses (established by a working group of GPs and psychiatrists) and their needs for collaboration with MHPro. PMHP were divided in 3 groups: “no need” for collaboration GPs-MHPro, “need unmet” (they need the collaboration, but they didn’t have it) and “need met” (collaboration achieved). Factors for “no need” and “need unmet” were analyzed using two multivariate logistic regressions and the characteristics of patients were analyzed using chi-square and ANOVA tests (Younes, 2005).

### **Mental health problems vs. mental health treatments... what help people are seeking for?**

A phone survey evaluated the opinion of 441 adults (randomly selected from two suburban districts near Paris) about help-seeking in case of mental health problems and about mental health treatments. 412 people who lived in France in the last 6 months, with no mental health problems in the last year, responded to a questionnaire based on CIDI-SF (a short screening-scale for mental illness in general population, used to detect depression and anxiety disorders), CAGE (used to detect alcoholism) and Oslo-3 (which evaluated the impact of social support). The differences between participant's characteristics (gender, age, education, marital status and profession) and their response were studied using Chi-square test (Kovess-Masfety, 2007).

### **Mental health services use in oro-facial injured people**

Trying to determine how many patients with oro-facial injury ask for help, another study compares patients' and providers' perspectives regarding psychosocial aftercare needs. 25 patients with oro-facial injury and 35 providers from OMS (Oral and Maxillofacial Surgery) and ENT (Otolaryngology) services in LAC+USC Medical Center (the University of California, Los Angeles) were asked about patient's interest/need in a program helping them with mental health problems (anxiety, depression, alcohol problems). The instrument had 19 items about barriers to aftercare (care after discharge from hospital of a patient recovering from an illness or operation) and an additional item about openness to receive it. Responses were measured in a scale from 1 "strongly disagree" to 4 "strongly agree". Data analysis had three phases: descriptive statistics for individual items for patients and providers; Fischer test to compare mean responses on each barrier item for patients and providers; X<sup>2</sup> to determine differences between demographic variables in patients (Chandra, 2008).

### **Difficulties in accessing care in patients with serious mental illness**

A section about the access to medical care in 156,475 patients with severe mental illness and a disability component in NHIS (National Health Interview Survey) was conducted in 1994-1995. Participants were asked about having a single/multiple regular/not regular source of medical care (family doctor, general practitioner, internist etc.) and about barriers to care. Chi square test was used to compare demographics (age, gender, race, education, income and health insurance) and logistic regression was used to examine diagnostic category (psychotic disorders, bipolar disorders, major depressive disorder, dementia, personality disorders and others severe disorders) (Bradford, 2008).

### **The delay for the untreated psychosis**

A two years study was trying to determine DUP (duration of untreated psychosis = the duration from the first psychiatric symptom to the treatment) in 74 patients with first psychotic episode

(diagnosed using ICD-10), in South Warwickshire, United Kingdom. The patients were divided in two groups: 28 patients with a longer DUP (>12 weeks) and 46 patients with a shorter DUP (<12 weeks). The groups were compared by socio-demographic characteristics (age, gender, ethnicity, living conditions, relationship status and employment). The clinical aspects counted were: premorbid functioning, acute/insidious onset, affective/ non-affective diagnosis and comorbidity of substance misuse. Data were analyzed using X2 test. (Thomas, 2009)

### **The distance to health care services – time, limits and costs for the veterans of USA**

Regarding the distance (in terms of time, effort and money), the research team from VHA (Veterans Health Administration – which provides healthcare for 7.8 million of the 25 million veterans - 36% of them are living in rural areas) visited 15 urban and rural primary care clinics in a period of 5 months, for the duration of one business day. They interviewed 101 veterans who had clinic appointments in that day (96 of them responded to quantitative questions about demographics, distance, healthcare and barriers to care and 42 completed a survey about access to healthcare, distance and barriers to primary and specialty care). Healthcare providers and staff were also interviewed regarding the impact of distance on VMA services use: from 114 clinical staff and providers included, 88 completed the quantitative survey and 64 were interviewed (Buzza, 2011).

### **Psychiatric patients profile in India**

Another study evaluated the pathway to care in persons with mental illness, considering the duration of untreated illness, total duration of illness, number of health care providers, socio-demographic characteristics and diagnosis of patients. The particularity in mental health services in India is that patients with mental illness can seek help where they want, for example faith healers. For a period of 2 months (January and February) in 2010, family members of patients with mental health illness were interviewed. In 76 patients (diagnosed using ICD-10) the Encounter Form was conducted by 2 psychiatrists (Jain, 2012).

### **Mental health in minority ethnic groups in USA**

In US, a study examined the use of mental health service among 6,359 Latinos (chosen because of their number in US population and because of their heterogeneity) diagnosed (using DSM-IV criteria) with mood, anxiety or substance use disorders. Variables studied were: age of immigration, years in the US, language and social preferences, ethnic identity, barriers to care and severity of mental illness. Data were collected from 2 waves of NES-ARC (National Epidemiologic Survey on Alcohol and Related Conditions). Trained interviewers questioned participants in 2001-2002 and 2004-2005 (Keyes, 2012).

### **The use of Internet instead of mental health services**

In our days, the Internet provides a multitude of information and possibilities. Online networks hosted by people without mental health training were studied as factors of low rates of treatment in patients with mental illness, in 2,532 respondents to the 2008 NSDUH (National Survey on Drug Use and Health), who affirmed that they didn't get the needed mental health counseling or treatment in the last 12 months. A list of factors about health beliefs (treatment effectiveness and handling symptoms), practical issues (time, affordability) and stigma (negative effects in community or employment) was evaluated in terms of being related to use of Internet support. R version 2.12.2 logistic regression was used on a sample of 86 persons who used Internet support group as an alternative to mental health treatment (Townsend, 2012).

### **The access to mental health care in patients with schizophrenia**

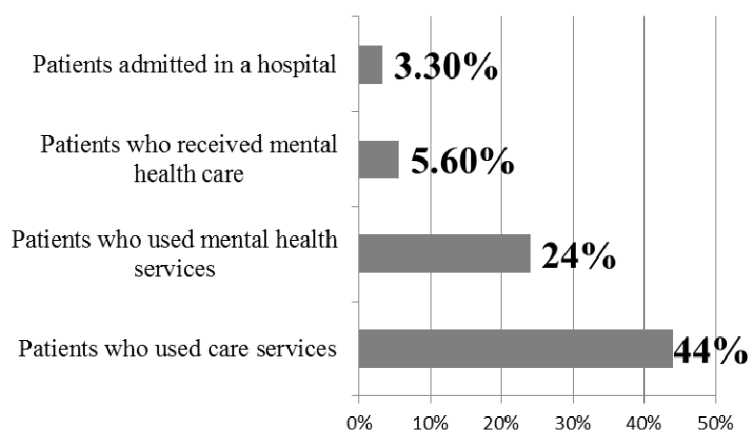
The factors influencing access to psychiatric treatment in patients with schizophrenia were evaluated using an interview schedule named SOFIAC ("Schedule of Factors Influencing Access"). SOFIAC interviews patients and family members using 15 items referring to multiple factors: patient related (knowledge and attitude towards psychiatric illness and treatment, opinion about the necessity of treatment, the presence or absence of insight and cooperation), family related (support, issues/dynamics, tolerance/acceptance of illness, resilience towards symptoms) community related (attitude and beliefs, acceptance and support), stigma, financial issues, distance/transport problems, gender, age and comorbidities of the patient. First, the participants were asked about the factors influencing patients with schizophrenia not to seek treatment. After that, they were asked to give details about each factor and questioned about the other factors stated by SOFIAC. All the responses were scored: 0 = "no influence", 1 = "some influence", 2 = "significant influence", 3 = "profound influence". The feasibility of the schedule was tested in 10 untreated patients with schizophrenia and their families. The schedule's validity (the comprehensiveness of the factors, scoring system, interviewing method, instructions and overall schedule) was evaluated by 12 experts (from the National Institute of Mental Health and Neuro Sciences, Bangalore) using Likert scales: 1 = "not at all satisfactory", 2 = "somewhat satisfactory", 3 = "neutral", 4 = "satisfactory" and 5 = "very satisfactory". All 12 experts rated the 5 aspects of SOFIAC with a score 4 (satisfactory) or higher (Reddy, 2013).

### **Assisting a person with mental illness in Australia – theory and practice**

The knowledge and skills of general population in assisting a person with mental illness were investigated in Australia, in 6,019 participants over 15 years old, who were asked how they would help a person with depression, suicidal thoughts, early and chronic schizophrenia, social phobia and PTSD (Post-Traumatic Stress Disorder), and their responses were compared to expert's guidelines on mental health first aid, evaluating both intentional and behavioral plan. 98.6% (5,937) answered the intentional questions and 2,615 responded to the behavioral questions. The study was based on

ALGEE action plan, a mnemonic plan about the first aid in mental health crises, which stands for: “Approach the person, assess and assist with any crises”, “Listen non-judgmentally”, “Give support and information”, “Encourage appropriate professional help” and “Encourage other supports”. A CATI (computer-assisted telephone interview) was conducted using The Social Research Centre, between January-April 2011. The participants were asked about demographic information and then they received a randomly male or female case-vignette of a person with mental health problems, based on DSM-IV and ICD-10 diagnostic criteria. Participants were also asked about their opinion on causes of mental illness and their knowledge about mental health organizations. Non-parametric tests were used for data analysis (Rossetto, 2014).

## Results and discussions



**Figure 2.** Results in Chile, in the last 6 months (Saldivia, 2004)

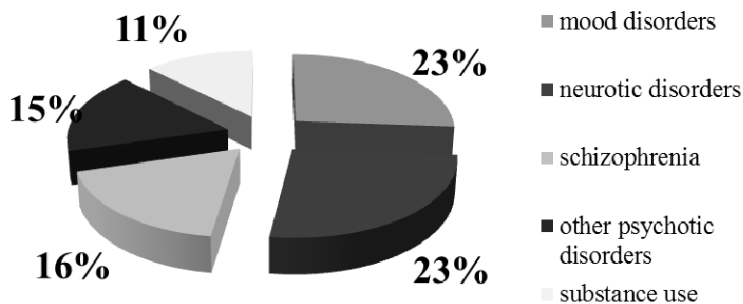
The prevalence of mental illness (in one year) in Chile was 19.3%. Almost a half (44%) of the participants used care services (in a half of cases - mental health services - 24%), but only 5.6% received mental health care in the last 6 months and 3.3% were admitted at least one day in a hospital. In the same time, 12.7% reported emotional problems and stated that they should have a medical consultation for a psychological problem. Non-specialized mental health care services were sought more often by women than men, and specialized mental health care were requested by respondents aged 55-64 more often than those aged 15-24.

The study showed that 62% of the respondents with psychiatric disorders have not received mental health care.

Among the factors influencing patients in seeking help for their mental health problem, the study revealed the impact of:

- A low level of education, which was associated with concerns about what others would think and the conception that the individuals should solve their own problems.
- A low level of income, associated with not knowing where to seek help, concerns about financial barriers, beliefs that mental health consult is a waste of time and their treatment is not helpful (Saldivia, 2004).

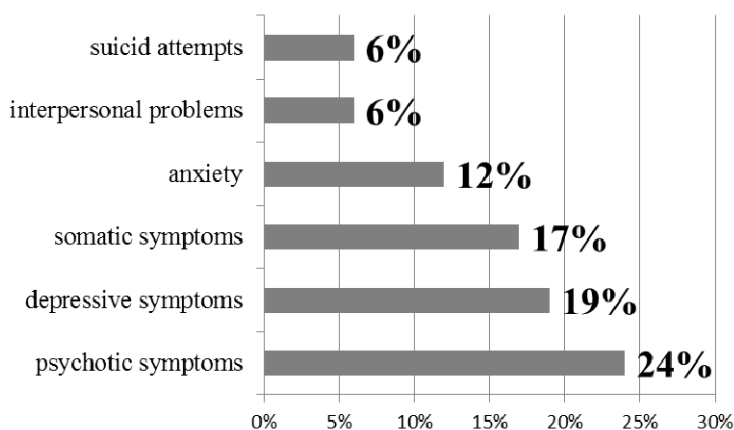
In the study realized by Gater et al., 28-38% of the respondents had psychiatric history and the most common diagnoses were:



**Figure 3.** Eastern Europe diagnosis (Gater, 2005)

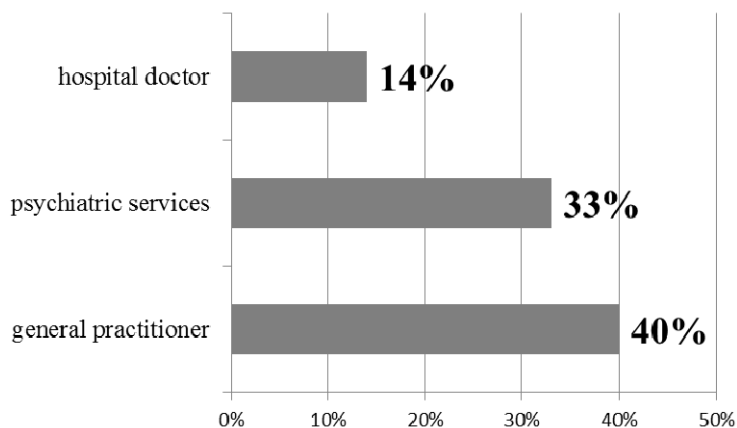
Family suggested the patient to seek care in 70% of psychotic symptoms, 100% of violent behavior situations and in 90% of suicide attempts and the duration from the first psychiatric symptom to the arrival at mental health services was shorter in patients with psychotic disorder than in others (the median duration was 3 weeks).

The main problem for the respondents was:



**Figure 4.** The main problem for the participants (Gater, 2005)

Patients asked for help from a doctor in 87%:



**Figure 5.** The first consults for psychiatric problems (Gater, 2005)

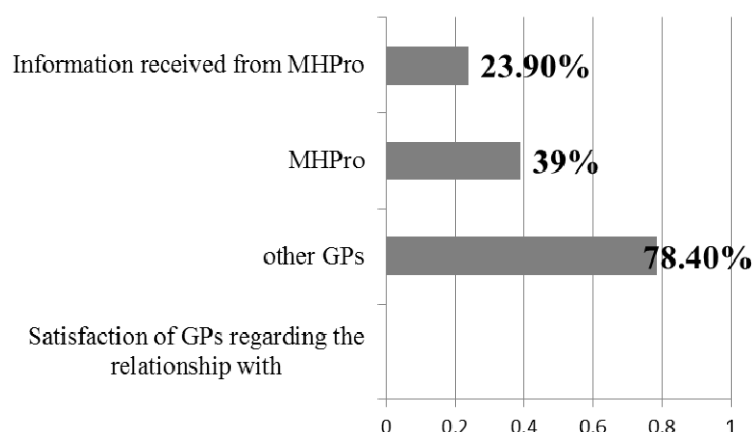
General practitioners were more often asked for help for psychiatric symptoms than the other doctors, including psychiatrists. This is an important result, because in more than a half of cases, general practitioner treated the patients with a sedative or hypnotic and 40% of the patients received no treatment from them (Gater, 2005).

If we take a look at another study (Younes, 2005), the GPs (general practitioners) managed 71.6% of the PMHP (patients “for whom a mental health problem was the main current problem”) for more than 2 years (a consultation lasted on average 23.2 minutes). 4 in 5 GPs considered that PMHP expect more care and require longer consults than the other patients and GPs regretted to have many PMHP in 64.2%. The majority of the PMHP were anxious (33.7%) or depressive (31.3%), with 6.7 years duration of the mental illness and history of psychiatric admission in 18.3% cases.

Considering the collaboration between different specialties, GPs declared that they are “very” or “mostly” satisfied by the relationship with other GPs (78.4%), but only half of them were satisfied by the relationship with MHPro (mental health professionals) and the information received from them was “mostly satisfying” in only 23.9% (Figure 6).

The need for collaboration with MHPro was felt by GPs in 43.3% (especially when the PMHP had past admissions in psychiatric services, when their problem were longer than one year and the GPs were younger) and their need was met in 35.5% of cases.

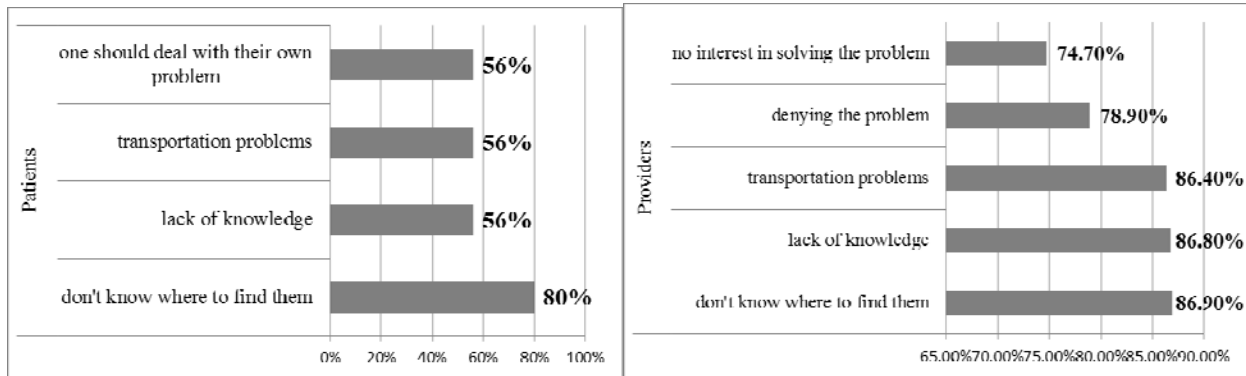
So many studies underline the importance of GPs in mental health care and of the relationship GP-MHPro: 57.8% of the participants would see the GP first, while only 15.1% would seek a psychologist and 14.6% would seek a psychiatrist. 46.6% would continue to see the GP in case of mental health problems and 79.1% would seek a psychiatrist’s help if it was recommended by their GP. Patients preferred psychotherapy instead of medication (81.1%) and men preferred family and friends instead of mental health professionals (Kovess-Masfety, 2007).



**Figure 6.** The collaboration GPs-MHPro (Younes, 2005)

The study realized on patients with serious mental illness (43% psychotic disorders, 39% bipolar disorders and 1.39% major depression) revealed difficulties in accessing care and not a regular source of medical care in those patients (Bradford, 2008).

Trying to see if there are any difficulties in accessing mental health care in patients with oro-facial injuries, Chandra et al reported that mental health problems are frequent (76% depression, 84% PTSD and 68% alcohol problems) and 84% of the patients were interested in psychosocial aftercare (Chandra, 2008). The barriers to psychosocial aftercare were:

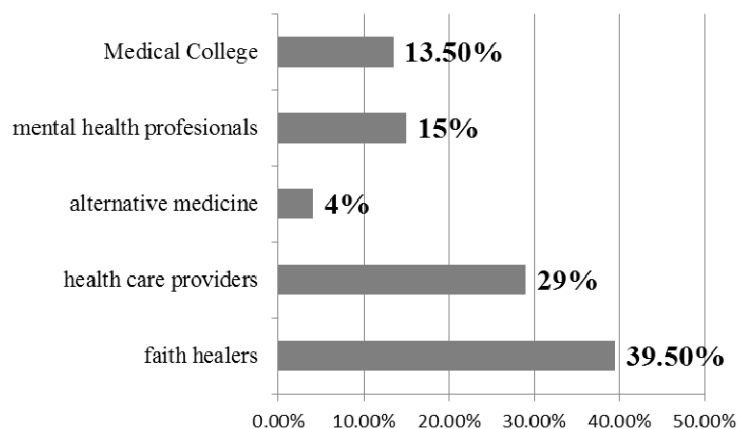


**Figure 7.** The barriers to care in patients vs. providers (Chandra, 2008)

So statistics showed that for certain people there are some barriers to mental health care and this involve sometimes a long delay to the first psychiatric consult: in Thomas’ study, the DUP (duration of untreated psychosis) mean was 19.47 weeks and the median was 4 weeks. A longer DUP was significantly associated with: male gender, unemployed, insidious onset, use of psychoactive drugs and no help seeking in families, while a shorter DUP was associated with acute presentation. An interesting fact was that there were no significant differences in age, ethnicity and diagnosis (Thomas, 2009).

The VHA (Veterans Health Administration) pointed out the importance of distance as a barrier to care: the patients traveled an average 44.5 miles (71.6 km) to a VHA clinic and the distance was the most frequent barrier selected by both patients and providers/staff, including “time”, “limited transportation” and “costs” (Buzza, 2011).

In India, patients sought for help in:



**Figure 8.** The first consults for psychiatric symptoms in India. As an observation, 12 patients searched help in faith healers after visiting psychiatrists and 12 patients – after visiting allopath care providers. (Jain, 2012)

The mean of total duration of illness was 48.8 months and the mean of duration of untreated illness was 36.76 months. The results showed that the duration of untreated illness and total duration of illness is lower in psychotic disorders than in other illnesses. Patients seeking help in psychiatric services were more likely young males, unmarried, educated, having a non-Hindu religion (Jain, 2012).

Trying to determine the role of ethnic and cultural factors as barriers to care, Keyes showed that less use of mental health services among persons with psychiatric illness was found in participants with strong Latino ethnic identity and Spanish language or Latino social preferences (after adjustments for severity of illness, years in US and age at immigration). Ethnic and cultural factors were found to be important barriers to mental health care for mood and anxiety disorders, but not substance use disorders among US Latinos (Keyes, 2012).

In a period where Internet is present everywhere, we considered important to remind the results of a study published by Reddy in 2013, which described 3 factors as being significant predictors for using Internet instead of mental health services (while stigma and gender were not significant factors):

- fear of admission or medication (8 times greater odds of Internet support group use);
- insurance problems (3 times greater odds of Internet support group use);
- age under 20 years.

We have to note that the mean age of patients was 38.2 and the mean duration of illness was 83.5 months.

Other factors which seemed to influence patients not to seek psychiatric treatment were related to:

- their family: good support, issues/dynamics, resilience towards symptoms;
- the community: attitude and beliefs, acceptance and support. **(Reddy, 2013)**

When we talk about practice, Rossetto et al revealed the next results: even if the majority of people would listen to a person with a mental health problem, support him/her and encourage him/her to seek for professional help, how to approach the person was not clearly stated and almost no participant provided details about how to “assess and assist the crises”. Even if the majority of participants stated the need to talk to the person and the need for support, only 140 offered details about how to do that (e.g. with empathy, validate their feelings) and the majority of them did not understand what type of support could be provided. Participants receiving depression or suicidal thoughts vignettes recommend professional help more likely than participants to the social phobia vignette. In all vignettes, participants received a higher score in depression and suicidal thoughts than in schizophrenia (Rossetto, 2014).

So the factors influencing patient access to psychiatric services, studied in 2004-2014, where:

- A lower level of education
- Low level of income
- Distance
- Family
- Stigma
- The impact of general practitioners
- Collaboration between general practitioners and mental health professionals
- Psychotic disorders
- Young males
- Unmarried
- Educated
- Religion
- Difficulties in accessing care
- No regular source of medical care
- Ethnic and cultural factors
- Internet
- Good support
- Resilience towards symptoms
- Attitude and beliefs
- Demographic characteristics
- The first aid lack of knowledge in mental health problems
- Lack of knowledge
- Transportation problems
- One's should deal their own problem

## Conclusions

Because of multiple factors (stigma, GPs, distance, time and costs, ethnic aspects, access to information etc.), there are still barriers to mental health care in our days. Multiple studies have proved that mental health services are continuously developing and regularly reevaluations of their evolution are needed all over the world.

## References

1. Bradford, D.W., Kim, M.M., Braxton, L.E., Marx, C.E., Butterfield, M. & Elbogen, E.B. (2008). Access to medical care among persons with psychotic and major affective disorders. *Psychiatric Services*, 59(8), 847-852.
2. Buzza, C., Ono, S.S., Turvey, C., Wittrock, S., Noble, M., Reddy, G., Kaboli, P.J. & Reisinger, H.S. (2011). Distance is relative: unpacking a principal barrier in rural healthcare. *Journal of General Internal Medicine*, 26(2), 648-654.
3. Chandra, A., Marshall, G.N., Shetty, V., Paddock, S.M., Wong, E.C., Zatzick, D., Luo, G. & Yamashita, D.D. (2008). Barriers to seeking mental health care after treatment for orofacial injury at a large, urban medical center: concordance of patient and provider perspectives. *The Journal of Trauma and Acute Care Surgery*, 65(1), 196-202.

4. Gater, R., Jordanova, V., Maric, N., Alikaj, V., Bajcs, M., Cavic, T., Dimitrov, H., Iosub, D., Mihai, A., Szalontay, A.S., Helmchen, H. & Sartorius, N. (2005). Pathways to psychiatric care in Eastern Europe. *British Journal of Psychiatry*, 186, 529-535.
5. Jain, N., Gautam, S., Jain, S., Gupta, I.D., Batra, L., Sharma, R. & Singh, H. (2012). Pathway to psychiatric care in a tertiary mental health facility in Jaipur, India. *Asian Journal of Psychiatry*, 5(4), 303-308.
6. Keyes, K.M., Martins, S.S., Hatzenbuehler, M.L., Blanco, C., Bates, L.M. & Hasin, D.S. (2012). Mental health service utilization for psychiatric disorders among Latinos living in the United States: the role of ethnic subgroup, ethnic identity, and language/social preferences. *Social Psychiatry and Psychiatric Epidemiology*, 47(3), 383-394.
7. Kovess-Masfety, V., Saragoussi, D., Sevilla-Dedieu, C., Gilbert, F., Suchocka, A., Arveiller, N., Gasquet, I., Younes, N. & Hardy-Bayle, M.C. (2007). What makes people decide who to turn to when faced with a mental health problem? Results from a French survey. *BioMed Central Public Health*, 7, 188.
8. National Institutes of Health, National Institute of Mental Health. (2005). *Mental Illness Exact Heavy Toll, Beginning in Youth*.
9. Reddy, K.S., Thirthalli, J., Kumar, C.N., Reddy, N.K., Renukadevi, N.R., Rawat, V.S., Ramkrishna, J. & Gangadhar, B.N. (2013). Schedule of factors influencing access to psychiatric treatment in persons with schizophrenia: validity and pilot testing. *Indian Journal of Psychological Medicine*, 39(4), 364-367.
10. Rossetto, A., Jorm, A.F. & Reavley, N.J. (2014). Quality of helping behaviours of members of the public towards a person with a mental health illness: a descriptive analysis of data from an Australian national survey. *Annals of General Psychiatry*, 13, 2.
11. Saldivia, S., Vicente, B., Kohn, R., Rioseco, P. & Torres, S. (2004). Use of mental health services in Chile. *Psychiatric Services*, 55(1), 71-76.
12. Shorter, E., (1997). *A History of Psychiatry From the Age of the Asylum To the Age of Prozac*
13. Substance Abuse and Mental Health Services Administration. (2012). Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings NSDUH Series H-42, HHS Publication No. (SMA) 11-4667). Rockville, Md.; Substance Abuse and Mental Health Services Administration, 2012
14. Thomas, S.P. & Nandhra, H.S. (2009). Early intervention in psychosis: a retrospective analysis of clinical and social factors influencing duration of untreated psychosis. *The Primary Care Companion to the Journal of Clinical Psychiatry*, 11(5), 212-214.

15. Townsend, L., Gearing, R.E. & Polyanskaya, O. (2012). Influence of health beliefs and stigma on choosing internet support groups over formal mental health services. *Psychiatric Services*, 63(4), 370-376.
16. World Health Organization (2001). Cross-national comparisons of the prevalences and correlates of mental disorders. *Bulletin of World Health Organization*, 78, 4.
17. World Health Organization, (2001) National Institutes of Health, National Institute of Mental Health. (n.d.). Statistics: Any Disorder Among Adults. *The World Health Report 2001 Mental Health: New Understanding, New Hope* Geneva
18. Younes, N., Gasquet, I., Gaudebout, P., Chaillet, M.P., Kovess, V., Falissard, B. & Hardy Bayle, M.C. (2005). General Practitioners' opinions on their practice in mental health and their collaboration with mental health professionals. *BioMed Central Family Practice*, 6, 18.

## THE ROLE OF PERSONALITY AND COPING STRATEGIES IN PSYCHOSOMATIC ILLNESSES

Annamária Porkoláb<sup>1,2</sup>, Adriana Mihai<sup>2,3\*</sup>

<sup>1</sup>Cosa and Porkolab Professional Civil Association of Psychology Mureş

<sup>2</sup>University of Medicine and Pharmacy, Targu Mures

<sup>3</sup>Institute of Psychotherapy and Personal Development (IPPD), Targu Mures

### **Abstract**

*Psychological factors involved in somatic disorders can cause, induce, further and intensify an organic disease. But very often organic diseases are also followed by psychological reactions that may influence the character or even the whole personality. Personality and coping strategies play an important role in the development of psychosomatic diseases. Restructuring dysfunctional coping strategies to positive and proactive strategies through psychotherapeutic interventions may further the improvement of the mental and clinical condition of the person.*

**Keywords:** *psychosomatic, coping strategies, proactive coping, personality, psychotherapeutic interventions.*

### **The concept of a psychosomatic disease**

The cause of increasing frequency of psychosomatic diseases could be the alert life that we live, the everyday stress. Psychosomatic disorders refer to those somatic disorders whose appearance and evolution is affected by psychological factors. Any condition of our body is influenced to some extent by psychological mediators (negative emotions, irrational thoughts, dysfunctional coping mechanisms, etc.), but there are some conditions for which this relationship between psychic and somatic is very obvious.

In a study of patients with asthma [1] it has been revealed that individuals suffering from asthma have poorly developed emotional quotient and their adaptability to stressful situations is lower. So becoming aware of emotions, a better understanding and an effective management on them could prevent the emergence of somatic diseases.

Another study [2] conducted on the types of behavior and personality in coronary heart diseases showed the following behavioral traits: very intense primary emotional reactivity, anxiety perceived as an undefined fear or panic attacks, aggression diverted most often onto themselves, extreme toughness and stubbornness, susceptibility, pride, egocentric tendencies.

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\* Correspondence: *Adriana Mihai*, IPPD Targu Mures, Romania. Tel.: +40365882188; e-mail: [ippdms@yahoo.com](mailto:ippdms@yahoo.com).

In a study [3] which assessed the relations of psychological factors in the prognosis of hyperthyroidism for people with Basedow-Graves autoimmune thyroidal disease who have had a drug treatment has shown that hypochondria, mental fatigue, depression and paranoia are predisposing factors for the recurrence of the disease.

Regarding the personality profile of people with psychosomatic diseases in a study [4] made by evaluating people suffering from different types of psychosomatic diseases (hyperthyroidism, hyper-calcemia, obesity, liver diseases, asthma, heart diseases, etc.) has shown that these people have a greater need of the approval of others, often have feelings of guilt, are tense and dependent, do not express their emotions, being afraid of refusal.

A Chinese proverb says that the secret to a long life is disease. The better we recognize the symbolic role of every disease of our lives and use effective coping mechanisms for external requirements, the more we stand a better chance for developing a psychic and somatic balance.

### **Coping mechanisms**

Coping is a process by which a person manages to adapt to the demands of everyday stressful events. A coping strategy is the way a person tries to restore a balance as a response to a stressful situation. The concept was introduced by Lazarus and Folkman, and refers to a cognitive and behavioral effort by which the person tries to reduce and master the internal or external demands that exceed their own resources [5]. Regarding the nature of coping there is a paradigm among researchers, some [6] believe coping is a stable trait, but others talk about the flexibility of the coping and consider it a developing process [7].

Folkman and Lazarus described coping as a dynamic process, and differentiated two styles of coping: a problem focused coping and an emotion focused coping [8]. Carver extended these two coping styles thus developing a multidimensional model of coping called COPE Inventory [9]. This inventory was further developed by Litman and includes dimensions such as: personal independence by focusing on the problem, personal independence with focus on emotions, avoidant coping and searching for social support [10].

This development of coping features got polished again, therefore Folkman and Lazarus established eight factors for the structure of coping: confrontation, distancing, self-control, searching for social support, taking the responsibility, escaping-avoidance, planning the problem solving, positive re-evaluation [11].

Positivist researches over the last decade have highlighted the existence of specific types of coping. One of these is the type of positive coping being an innovative approach in psychology and psychotherapy that emphasizes the potential benefits of positive feelings [12] and refers to looking for a positive significance during stressful events. Another positivist approach is the theory of

proactive coping [13] includes self-regulating strategies for achieving goals and the concept of personal development.

The two types of coping previews the need for therapeutic interventions in the life of each person in order to develop functional and effective coping strategies.

### **The relationship between personality and coping**

The manifestation of a disease depends on the whole psyche of the person, and is influenced by their personality (character, temperament). But this may also be the other way around, organic diseases are often accompanied by psychic reactions which may affect the character or the entire personality.

In thyroid dysfunctions a high level of fatigue and irritability can be manifested. This way studying the relationship between coping mechanisms and personality becomes important.

A recent study [14] highlighted the fact that coping mechanisms geared actively towards solving the problems correlated with the dimensions of personality such as openness, extraversion, and sociability. There is a strong correlation also between the relational dimension of the personality (sociability), and the search for social support.

Another study [15] shows a positive correlation of neurosis with coping mechanisms focused on negative emotions that are actually avoidant or indirect coping strategies, and that extroverted people face multiple stressful situations with emotionally positive coping mechanisms, often using the interpersonal relationships as a personal support. Neuroticism predisposes people to interpersonal stress and conflicts, and neurotic people tend to evaluate events as very threatening, and their coping resources are very low.

Personality and coping strategies play an important role in the development of psychosomatic diseases. Restructuring dysfunctional coping strategies to proactive strategies through psychotherapeutic interventions may promote the improvement of the mental and clinical state of a person.

### **References**

1. Ropoteanu, A.C., Iamandescu, I.R., (2010), Emotional intelligence, asthma and emotions, Romanian Journal of Medical Practice. 2010, Vol. 5 Issue 4, 265-271. 7p. 1 Chart.
2. Onofrei Rodica Maria (2008), The correlation between the type of behavior and responsiveness to coronary heart disease, AMT, vol II, nr. 3, 50.
3. Fukao A, Takamatsu J, Murakami Y, Sakane S, Miyauchi A, Kuma K et al. (2003) The relationship of psychological factors to the prognosis of hyperthyroidism in antithyroid drug-treated patients with Graves' disease. *Clinical Endocrinology* 58:550–555.

4. Simona Trifu (2011) Mental Fragility and Psychosomatic Illness, Romanian Journal of Psychiatry, vol. XIII, No.1, 37-44.
5. Lazarus, R.S., Folkman, S. (1987) Transactional Theory and Research on emotions and coping, European Journal of Personality, 1, 141-169.
6. Miller, S. (1987) Monitoring and blunting: validation of a questionnaire to assess styles of information seeking under threat, Journal of Personality and Social Psychology, 52, 345-353.
7. Lazarus, R.S., Folkman, S. (1984) Stress, Appraisal and Coping, Springer Publishing Company, New York.
8. Folkman, S., Lazarus, R. S. (1985), If it changes it must be a process: study of emotion and coping during three stages of a college examination., Journal of Personality & Social Psychology, 48, 150-170.
9. Carver, C.S., Scheier, M. F., & Weintraub, J. K. (1989) Assessing coping strategies: A theoretically based approach. Journal of Personality and Social Psychology, 56, 267-283.
10. Litman, J. A. (2006), The COPE inventory: Dimensionality and relationships with approach- and avoidance-motives and positive and negative traits., Personality and Individual Differences, 41, 273-284.
11. Popa-Velea O. (1999) Adaptive coping mechanisms and implications in medical practice, Elements of General and Applied psychosomatics, Infomedica.
12. Seligman Martin E. P, Csikszentmihalyi Mihaly (2000), Positive Psychology, American Psychologist, Vol 55. No. 1. 5-14.
13. Schwarzer, R., Knoll, N. (2002). Positive Coping: Mastering Demands and Searching for Meaning, S.J. Lopez, C.R. Snyder (Eds.), Handbook of Positive Psychological Assessment. Washington, DC: American Psychological Association.
14. Atefe Karimzade, Mohammad Ali Besharat, An investigation of the relationship between personality dimensions and Stress coping styles, Procedia - Social and Behavioral Sciences 30 2011, 797-802.
15. Ming Sing Chai, Chee Seong Low, (2015), Personality, Coping and Stress Among University Students, American Journal of Applied Psychology; 4(3-1):33-38.

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