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**CAREGIVERS OF PATIENTS WITH MAJOR NEUROCOGNITIVE
DISORDER: EMOTIONAL AND BEHAVIORAL DISORDERS
(BURNOUT)**

ABSTRACT OF DOCTORAL THESIS

PhD supervisor:

PROF. UNIV. DR. HABIL. CIOBANU ADELA MAGDALENA

Doctoral candidate:

DR. DAMIAN ANA CLAUDIA

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The general part

In this section of the doctoral thesis, I described the neurocognitive disorders, defined and highlighted the role of the informal caregiver, followed by the description of the concept of burnout and the pandemic context during the research period.

ICD 10 (International Classification of Disorders 10th Edition) defines dementia as a chronic, progressive brain disorder in which there are disturbances of several higher cortical functions such as memory, thinking, orientation, comprehension, calculation, learning ability, language and judgment, but consciousness is not affected. Impairment of emotional control, social behavior or motivation is sometimes preceded by cognitive impairment [1].

Added to the number of cases of patients with Alzheimer's dementia in Romania (270-300,000 people), there are 3-4 people/patient as caregivers and we can say that for them the quality of life is deeply disturbed, totaling approximately 1 million people, not to mention the cases cared for by their family and undiagnosed [2]. In 2015, official figures confirm a number of 600,000 Romanians with Dementia [3].

In the early stages patients are still independent, as they can walk alone, participate in social activities and volunteer. The role of carers is to help them stay as independent as possible. All these characteristics can be overwhelming because of the obstacles that await in the future.

The longest stage is the intermediate stage, which can last for years. At this time, caregivers' responsibilities increase as patients begin to have difficulty communicating, require help dressing, become irritable, short-tempered, or display strange behaviors such as refusing to bathe. At this time, the main problems that arise include: memory disorders, mood changes (depression, anxiety, irritability), behavioral changes, repetitive actions, sleep disorders, tendency to wander alone, physical or verbal heteroaggression, communication disorders, require help with daily activities, hallucinations, delusional ideation and suspiciousness.

In the last stage, they have difficulty chewing and swallowing food, they require support to walk and are susceptible to infections, such as pneumonia. At this stage of the disease, when the patient becomes completely dependent, the caregiver's role is to maintain the patient's quality of life and dignity. The increasing needs of this period can exceed the capabilities of home care, which is why relatives turn to care centers [4].

Caregivers, often called "secondary invisible patients", significantly improve the quality of life of people diagnosed with major NCD (Neurocognitive Disorder), who ultimately require an increased level of attention, and most caregivers are members of family or friendship groups. Studies show that the majority of the caregiver population consists of patients' husbands or wives, followed by children or daughters-in-law, sons-in-law, who are mostly female [5].

Over time, caregivers begin to experience mood disorders (anxiety and depression). Female gender, degree of close kinship with the patient, additional stressful events, health status,

hereditary history of psychiatric disorders, quality of the caregiver-patient relationship, low self-esteem, and severity of the patient's behavioral and psychological disorders are risk factors [6 , 7].

The chronic stress associated with the responsibilities of informal caregiving predisposes them to the apathy of the burnout syndrome. Usually, patients are cared for by family members who, most frequently, have no way of sharing their responsibilities, which can lead to emotional exhaustion, in contrast to care provided by formal caregivers [8]. As emotional the physical and mental deterioration of a loved one is, caring for them during difficult times (agitation, tendency to wander, shameful behavior) is even more difficult.

During the course of the doctoral research, the SARS-Cov2 pandemic (severe acute respiratory syndrome due to the coronavirus) left its mark on the global population, but the biggest effects were recorded in the elderly population, including patients with major NCD.

Since December 2019, when the first cases of infection with this virus were reported, the infectivity, the incubation period, the symptoms have been established (which vary from asymptomatic or no symptoms to fever, cough, muscle pain, breathing difficulties, pneumonia and distress syndrome).

The World Health Organization declared a pandemic in March 2020, due to the speed with which the virus spread [9].

Elderly patients or patients with other associated conditions were at increased risk of infection with COVID-19. In addition, most of them have other chronic diseases such as diabetes, obesity, hypertension and cardiovascular diseases. Cognitive impairment in dementia patients prevents them from understanding and implementing preventive measures such as social distancing, wearing masks and frequent hand disinfection [10].

I. Personal contributions

Objectives and hypothesis

The main aim of this research is to assess emotional and behavioral disturbances (burnout) in a group of informal caregivers of patients with major NCD.

The secondary objectives of this research are to identify the biomarkers of burnout described in the specialized literature, to describe the typical informal caregiver profile of patients with major NCD during the pandemic, to assess the difficulties and needs of informal caregivers during the COVID-19 pandemic, to measure the level of depression, anxiety, burnout and the quality of life of informal caregivers, the evaluation of the fear of COVID and its influence on the quality of life, the predictors of changes in quality of life of informal caregivers.

Study design

The present study was a prospective one carried out for 6 months, including a group of informal caregivers of patients diagnosed with dementia, selected from the register of those hospitalized in the "Prof. Dr. Al. Obregia" Hospital, First Clinical Department, between 2020-2021.

Caregivers were contacted by telephone during 2021-2022 to be invited to participate in this study, with the aim of being assessed according to the eligibility criteria and to explain the conditions necessary for participation. Those who agreed to participate were contacted by the principal investigator who monitored the assessments.

The included participants were assessed 3 times during the 6-month period (at inclusion in the study, at 3 months and at 6 months) through a questionnaire administered by telephone by an investigator, which analyzed the socio-demographic profile, difficulties and needs of caregivers during the pandemic and tested for burnout, anxiety, depression, quality of life, fear of COVID, sleep quality and caregiver burden.

The research was carried out according to the Declaration of Helsinki, with the approval of the Ethics Committee of the Clinical Hospital of Psychiatry "Prof. Dr. Al. Obregia" (No. 73/7.10.2021).

Measurement instruments

The questionnaire applied to the caregivers included in the study was composed of the following:

- Socio-demographic data: gender, age, place of origin, marital status, number of children in care, education, profession, occupation and the way it is carried out (online/physical/both)

- Data related to the patient cared for: "How many people are caring for the patient?, What is the complete diagnosis of the patient?, What is the last MMSE (Mini mental state examination) score of the patient?" What is your degree of kinship with the patient?"
- Data related to COVID infection: "Have you had COVID? Are you vaccinated?"
- Open questions about caregivers' problems: "What difficulties did you encounter during the pandemic? What kind of support did you need?"
- Maslach burnout questionnaire (Maslach Burnout Inventory- MBI—General Survey): This is a psychological assessment tool that includes 22 items, with 7 answer options [11].
- The Hamilton anxiety rating scale: the purpose of the questionnaire is to analyze the severity of anxiety [12].
- The Hamilton Depression Rating Scale (HAM-D). Over time, it became the most widely used depression assessment tool [13].
- The questionnaire for the quality of life created by the World Health Organization (World Health Organization Quality of Life Bref 26 - WHOQOL BREF 26) - is a questionnaire with 26 items, which measures the quality of life by evaluating 4 components: Physical health, mental health, social relations, environment [14].
- The questionnaire for the quality of sleep (Pittsburgh sleep quality index - PSQI) - is a questionnaire that evaluates the quality of sleep over a period of 1 month. [15].
- The fear of COVID questionnaire (Fear of COVID scale) [16].
- Caregiver burden scale questionnaire – made up of 15 items that describe the assistance provided to the patient [17].

Selection of participants

To participate in the study, the following inclusion criteria were applied:

1. the participant is an informal caregiver of the patients hospitalized in the Psychiatric Hospital "Prof. Dr. Al. Obregia" from Bucharest, Romania;
2. the participant agreed to participate in the study and signed an informed consent;
3. the participant is an informal caregiver of a patient with a diagnosis of dementia, excluding dementia with Lewy bodies;
4. the participant has no history of substance abuse in the 12 months prior to study participation.

The exclusion criteria applied:

1. formal caregivers;
2. informal caregivers of patients diagnosed with dementia with Lewy bodies;
3. participants were diagnosed with psychiatric illness or history of substance abuse in the past 12 months prior to participation in this study.

Statistical analysis

The telephone questionnaire was recorded using Google Forms, one form for each stage, and later 3 databases were created in Microsoft Excel with the results of the form.

The IBM Statistical Package for Social Sciences (SPSS) software, version 20, was used to perform the statistical analysis. The mean and standard deviation were used for the quantitative data, and the frequency and the percentage for the qualitative data.

The interpretation of the results was carried out by several t-tests and ANOVA tests (for analysis of variance), and multiple linear regressions were used to analyze predictor factors. The stepwise method was used to create multiple linear regression models.

WHOQOLBREF 26 total score was the dependent variable, and their professional efficacy, cynicism, burnout, anxiety, depression, caregiver burden, and sleep quality were independent or predictor variables. A threshold value of $p < 0.05$ was considered for statistical significance.

Association between burnout and immunological and endocrine alterations

In this review of the specialized literature, using the PubMed database, immunological and endocrine imbalances were identified in patients diagnosed with burnout. The following have been described for this: Cortisol, Corticotrophin-releasing hormone (CRH), Adrenocorticotrophic hormone (ACTH), Dehydroepiandrosterone (DHEA), Thyroid hormones, Dopamine and prolactin, Brain-derived neurotrophic factor (BDNF), Burnout, anxiety, depression and inflammation.

Assessment of the function of the hypothalamic-pituitary-adrenal axis is the most common and sensitive method to highlight the reaction to burnout, and most studies initially used cortisol as a marker, but the results were inconsistent due to its increased circadian and diurnal variations, but also inter-individual and intra-individual variability

Another level of investigation in patients with burnout is measuring ACTH levels because differences in cortisol production are easier to detect when testing reactivity and not resting levels of this hormone.

Since it is CRH that stimulates the production of ACTH, recent studies have investigated the link between these hormones and burnout.

Another physiological response to stress includes the release of anabolic hormones. Although few studies have focused on them, the most studied is DHEA.

The hypothalamic-pituitary-thyroid axis stimulates the secretion of thyroid hormones (T3, T4). Prolonged stress causes this axis to be less active, with significantly lower hormone levels.

The dopaminergic system controls energy expenditure, response vigor, and cognitive control functions, thus signs and symptoms of exhaustion suggest a decline in dopaminergic function.

BDNF has been studied in conditions such as depression and anxiety.

Studies have found a link between burnout and high levels of anti-inflammatory cytokines and low levels of pro-inflammatory cytokines.

The results of this study show us that burnout has multiple effects on the body, both microscopic (endocrinological and inflammatory changes) and macroscopic (affective symptoms leading to anxiety and depression). Our results indicate possible changes that burnout can induce in neuroendocrine and immune pathways.

Caregiving for Dementia Patients during the Coronavirus Pandemic

For this descriptive, cross-sectional study in the Romanian population, we conducted a telephone survey in 2022 with a series of questions addressed to a group of informal caregivers of patients with dementia admitted in the previous year at the "Prof. Dr. Al. Obregia" from Bucharest, Romania.

The initial assessment included a series of questions related to the caregiver's profile (age, gender, background, marital status, education, type of professional activity), followed by a series of open-ended questions related to COVID-19. Later, the following scales were applied: Test for measuring the quality of life - WHOQOL BREF, Fear of COVID-19 Scale.

A total of 156 participants answered the questionnaire, most of them women (88.5%, N = 138), living in Bucharest (41%, N = 64), with a high level of education (university 53.8%, N = 84), married (57.6%, N = 90) or in a relationship (20.5, N = 32), and with a job that requires physical presence (41%, N = 64).

The majority of participants had not been quarantined (63%, N = 98) or diagnosed with the illness (68%, N = 106).

During the COVID period, the majority of participants reported difficulty accessing medical services (35.9%, N = 56) and a worryingly high number of caregivers reported the death of the patient they were caring for (19.3%, N = 30).

When asked about other difficulties encountered, socio-professional problems were reported by the majority of participants (64%, N = 100), followed by emotional problems (34.6%, N = 54).

Based on mean values calculated for the four WHOQOL domains, participants scored lowest in the domain of social relationships (9.94), followed by mental health (20.76).

ANOVA test revealed a significant difference in education level and total scores for physical health ($F(2,152) = 4.64, p = 0.01$), mental health ($F(2,153) = 6.18, p = 0.003$) and quality of life ($F(2,153) = 4.61, p = 0.01$). Participants with postgraduate degrees scored higher in physical health (24.67, $p = 0.01$ and 24.48, $p = 0.01$) and mental health (20.67, $p = 0.002$; 19.82, $p = 0.008$) compared to high school graduates.

The fear of COVID was associated with the way of carrying out the activity in the work field. According to the ANOVA test, using the total score of the Fear of COVID questionnaire ($F(3,152) = 6.96, p = 0.001$), participants who needed physical presence to work obtained lower scores compared to those who worked online (20.76, $p = 0.001$), or even hybrid (16.65, $p = 0.01$).

Caregivers who reported emotional problems during this period had lower scores in physical health (23.85, $p = 0.03$), mental health (19.59, $p = 0.04$), social relationships (8.63, $p = 0.001$) and quality of life (78.96, $p = 0.001$). $p = 0.01$), but they had a higher score on the Fear of COVID questionnaire (16.65, $p = 0.01$).

Caregivers who reported socio-professional problems scored lower on the socio-professional dimension (9.52, $p = 0.01$) and quality of life (81.40, $p = 0.03$), but scored higher high on the Fear of COVID scale (18.64, $p = 0.001$).

Caregivers who reported financial problems scored lower on the Fear of COVID scale (14.33, $p = 0.03$) and the social relationships dimension (7.67, $p = 0.04$) (Table 8.6). In general, the category of participants with emotional, socio-professional and financial problems (category 2), as well as participants with COVID infection (category 4) recorded the highest scores on the Fear of COVID questionnaire.

For quality of life, all components had positive and strong relationships because they were components of quality of life, and for COVID, there were weak and negative relationships, highlighting that fear of COVID and environmental health do not influence each other.

Quality of life ($F(2,153) = 8.75, p = 0.001$) was influenced by fear of COVID and caregivers' emotional problems. Thus, both fear of COVID (beta = -0.25, $t = -3.29, p = 0.001$) and emotional problems (beta = -0.16, $t = -2.06, p = 0.04$) of caregivers negatively influenced the quality of life. Moreover, the variance explained by fear of COVID and emotional problems was 10%.

Physical health (beta = -0.36, t = -4.83, p = 0.001) and mental health (beta = -0.31, t = -4.05, p = 0.001) were negatively influenced by fear of COVID, and social problems were negatively influenced by emotional (beta = -0.33, t = -4.49, p = 0.001) and socio-professional problems (beta = -0.20, t = -2.67, p = 0.008) of participants. Furthermore, the variance in physical health explained by caregivers' fear of COVID was 13%, and fear of COVID explained 9% of the variance in mental health. Emotional and socio-professional problems explained 15% of the variance in social relationship health.

Quality of Life Predictors in a Group of Informal Caregivers during the COVID-19 Pandemic

For this prospective and longitudinal study, we conducted a telephone survey during 6 months, between 2021 and 2022, applying a set of questionnaires to a group of informal caregivers of dementia patients hospitalized between 2020 and 2021 at "Prof. Dr. Al. Obregia Psychiatry Hospital" from Romania.

Participants were assessed at three time points over six months: the first stage (S1) was at their inclusion in the study; the second stage (S2) was three months after the initial assessment; the third stage (S3) was six months from baseline.

The assessment of informal caregivers consisted of a series of questionnaires using the validated version in Romanian, as follows: socio-demographic data, questions regarding the COVID vaccination, questions regarding the patient with dementia, the Maslach Burnout Inventory, the Assessment Scale of Hamilton Anxiety Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), World Health Organization Quality of Life Questionnaire Short Version (WHOQOL bref 26), Pittsburg Sleep Quality Index (PSQI), Fear of COVID Scale -19, Burden of caregivers.

A total of 110 caregivers responded to the questionnaire, mostly women (N = 78, 70.9%), with an average age of 55.2 years, living in an urban area (N = 88, 80%), married (N = 76, 69.1%), with high school education (N = 58, 52.7%), employed (N = 68, 61.8%), and with a job that requires physical presence (N = 48, 43.6%).

Each patient had between one and four informal caregivers, the majority being their son or daughter (N = 68, 61.8%), followed by their wife or husband (N = 20, 18.2%). More than half of the patients were diagnosed with a mixed form of dementia (N = 64, 58.2) and had a mean MMSE score of 13.32 out of 30. The caregiver burden scale was also included in this part, as it illustrates the help provided by the patient's caregivers. In this case, the average score was 11.

Our caregivers had a high vaccination rate (N = 80, 72.7%) correlated with a low infection rate (N = 22, 20%), while patients had a vaccination frequency of 52 (47, 3%) and a low infectivity rate (N = 8, 7.3%).

During the COVID pandemic, 30.9% of informal caregivers indicated numerous problems (emotional, financial and physical). More than a quarter of individuals reported socio-professional problems (12.73%) or disease progression of the patient cared for (12.73%). Finally, some of them mentioned the difficulty of accessing the health system (7.27%) and a lack of patient compliance with the imposed restrictions (5.45%)

When asked about the desired support, the most frequently expressed were physical help (25.45%), more accessible nursing homes (14.55%) and financial (10.91%) or psychological support (10.91%).

A total of 110 caregivers were included in the first stage. The vast majority of participants reported low levels of burnout (N = 104, 95.5%), low levels of cynicism (N = 70, 63.6%), high levels of professional efficacy (N = 108, 98.2%), mild anxiety (N = 38, 34.5%), moderate-severe anxiety (N = 30, 27.3%), no depressive symptoms (N = 60, 54.5%), severe depression (N = 28, 25.5%) and a satisfactory level of sleep quality (N = 84, 76.4%), with an average quality of life score of 58.71.

The 96 participants included in the second stage had a low burnout rate (N = 84, 76.4%), a low level of cynicism (N = 42, 38.2%), a high degree of professional efficacy (N = 96, 87.3%) and a modest level of anxiety (N = 32, 29.1%), some members experienced severe anxiety (N = 30, 27.3%) and less than half of the participants reported no depressive symptoms (N = 50, 45.5%) or satisfactory sleep quality (N = 68, 61.8%), with a mean quality of life score of 57.40.

Finally, the 78 participants included in the final stage reported minimal burnout (N = 58, 52.7%), high levels of cynicism (N = 36, 32.7%) and high professional efficacy (N = 76, 69.1%). The level of anxiety increased (N = 28, 25.5%), while the level of depression remained stable (N = 40, 36.4%). Sleep quality was satisfactory (N = 46, 41.8%) and the mean quality of life score was 56.82.

Assessment of burnout levels using the ANOVA test comparing scores between the three time points indicated an increase in burnout levels, $F(2, 154) = 17.007, p = .001$, with the highest level at 6 months. Similar advances could be found in the cases of cynicism, $F(2, 154) = 21.824, p = 0.001$, and professional efficacy, $F(2, 154) = 11.892, p = 0.001$.

More than half of individuals (50.9%) reported mild or moderate anxiety, while 27.3% reported significant anxiety at baseline. Results of the ANOVA test showed stationary anxiety scores across the three time points, $F(2, 154) = 0.551, p = 0.57$ (scores between 13 and 13.66).

At baseline (S1), 25.5% reported moderate-severe depression and 20% mild-moderate depression. The evolution of the total score was also stationary from baseline to 6 months, $F(2, 154) = 2.738, p = .068$, with scores between 12.28 and 13.84.

A total of 23.6% of participants reported poor sleep quality at baseline, compared to 29.1% at 6 months. The evolution of sleep quality, $F(2, 154) = 6.236, p = 0.002$, showed

statistically significant changes between 3 months (lowest scores: 3.8) and 6 months (highest scores: 4.5).

Fear of COVID Scale results between baseline and 6 months were also statistically significant, $F(2, 154) = 25.701$, $p = .001$, with scores decreasing over time.

Results indicate a decrease in quality of life between the three reported time points, $F(2, 154) = 3.369$, $p = .03$, from baseline (58.66) to 6 months (56.82).

According to linear regression, the quality of life at baseline was influenced by the variables included in the model ($F(7, 102) = 44.05$, $p = 0.001$). Thus, the predictors for quality of life at baseline were cynicism at baseline ($\beta = -0.31$, $t = -2.35$, $p = 0.02$), anxiety ($\beta = -0.40$, $t = -2.97$, $p = 0.004$) and depression ($\beta = -0.50$, $t = -3.45$, $p = 0.001$). These predictors explained 73.4% of the variance in quality of life at baseline.

Quality of life at 3 months was influenced by variables included in the model ($F(6, 89) = 100.078$, $p = 0.001$). Thus, the predictive factors for quality of life at 3 months were cynicism at 3 months ($\beta = -0.44$, $t = -2.79$, $p = 0.006$), professional inefficiency at 3 months ($\beta = 0.46$, $t = 3.08$, $p = 0.003$), and depression at 3 months ($\beta = -0.82$, $t = -5.68$, $p = 0.001$). These predictors explained 86.2% of the variation in quality of life at 3 months.

At 6 months, quality of life was influenced by the variables included in the model ($F(6, 71) = 93.3r1$, $p = 0.001$). Thus, the predictive factors for quality of life at 6 months were cynicism at 6 months ($\beta = -0.46$, $t = -2.27$, $p = 0.02$), depression at 6 months ($\beta = -0.94$, $t = -6.21$, $p = 0.001$) and sleep quality at 6 months ($\beta = 0.21$, $t = 2.54$, $p = 0.01$). These predictors explained 87.8% of the variation in quality of life at 6 months.

Conclusions and personal contributions

In this doctoral thesis, the proposed objectives were evaluated, but not all hypotheses were confirmed.

The main research objective of this doctoral thesis was to evaluate emotional and behavioral disorders (burnout) in a group of informal caregivers of patients with major NCD in Romania.

Most biological markers of burnout belong to the HPA axis, but thyroid hormones, prolactin, or certain inflammatory markers have also been investigated.

From the category of HPA axis hormones, the most used in research studies was cortisol, due to the possibilities of collection (saliva, blood or hair), but due to inter-individual and intra-individual variability, the conclusions of the studies are heterogeneous.

The respondents of our questionnaire participated in defining the typical profile of an informal caregiver. The results show us that in general patients with dementia are helped by their

daughter, aged between 50-60 years, living in an urban area, married, having their own family to care for, with high school or higher education, employed in a job where physical presence is required during the pandemic and who share caring responsibilities with two or three other caregivers.

Most of the participants in the study reported emotional, financial and physical problems, but also low accessibility to the health system (difficulties accessing hospitals, interruption of specialized medical care and frequent testing of the COVID antigen at each consultation).

Caregivers reported the additional stress felt as a result of the patient's worsening cognitive deficit and behavioral changes, emergence of negative feelings, lack of support, and the imposition of COVID restrictions on an already uncooperative patient with absent disease awareness.

With the COVID pandemic, caregivers felt increased stress levels due to social isolation, sudden changes in their daily routine, feelings of loneliness or lack of therapeutic follow-up, fear of spreading the virus to their loved ones, feelings of helplessness and irritability.

Another category of difficulties was represented by the division of time between the activity at work and the care of the patient who needed constant supervision.

The needs expressed by the study participants were physical help in carrying out daily activities, accessible nursing homes, financial and psychological support.

At baseline, regarding the 3 components of burnout, the included participants presented low levels of exhaustion, cynicism, but high levels of professional efficiency, mild or moderate-severe anxiety. Most reported no depressive symptoms, but a significant percentage reported severe depressive symptoms. Sleep quality was satisfactory and caregivers reported an average quality of life score.

At the 3-month assessment, the level of burnout did not show changes through its 3 dimensions, but the level of anxiety became moderate, some of them even showing severe anxiety, and the number of those who showed depressive symptoms increased. Sleep quality decreased and quality of life remained somewhat constant.

After 6 months from baseline, participants reported high levels of cynicism and increased levels of anxiety. Depressive symptom severity, sleep quality, and quality of life remained constant.

Caregivers had a high rate of COVID vaccination that was also correlated with a low rate of infectivity. Study participants reported a low level of worry about COVID infection, which decreased further over the 6 months, consistent with the initiation of the vaccination program. However, those who reported emotional problems also reported a level of greater concern for COVID infection.

According to statistical analysis (linear regression) quality of life at baseline was influenced by cynicism, anxiety and depression, these factors explaining 73.4% of the variance in quality of life. Over 3 months, quality of life appears to have been influenced by cynicism, professional ineffectiveness, and depression, with these explaining 86.2% of the variance in quality of life. At 6 months, cynicism, depression and sleep quality explained up to 87.8% of the variation in quality of life.

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