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Research Article

Non-pharmacological Interventions for the Apathy in Patients with Dementia. A Cross-over Randomized Controlled Trial

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Abstract

Background: Apathy is associated with greater caregiver burden and affects the cognitive abilities of the patient. Having a high prevalence of more than 71% in patients with dementia (PwD), it is a very common symptom in Alzheimer's Disease (AD). In many cases it remains under-diagnosed or is misdiagnosed with depression.

Methods: This study is a cross-over randomized controlled trial with 60 participants conducted in Greece. The participants were randomly assigned in 6 different groups of 10 participants each. The interventions that were evaluated are: a) Body Exercise (BE), b) Reminiscence therapy (RT) and c) Music therapy (MT). The interventions lasted for 5 days and there was two days off, as a wash-out period. There was no drop-out rate. The measurements which were used at baseline were: MMSE, ACE-R, GDS, FRSDD and NPI questionnaires.

Results: The most effective combination was in order: RT- BE- MT. RT when applied in the first week reduced apathy statistically significant ($p = 0.007$). BE when applied in the second week reduced the symptoms further ($p = 0.013$) and MT when applied in the third week reduced apathy even more ($p = 0.027$). We had about the same results with the caregivers' burden following the same order of interventions: RT ($p = 0.006$)- BE ($p = 0.016$)- MT ($p = 0.030$).

Conclusion: A combination of a cognitive intervention (RT) in the first week, followed by BE the second week and a sensory intervention (MT) the third week, can reduce apathy in PwD and their caregivers' burden, as well.

Keywords: Apathy; BPSD; Dementia; Cross-over Trial; Non-pharmacological Interventions; RCT; Reminiscence Therapy; Body Exercise; Music Therapy

Abbreviations

ACE-R: Addenbrooke's Cognitive Examination; AD: Alzheimer's Disease; AES: Apathy Evaluation Scale; ACC: Anterior Cingulate Cortex; AP: Apathy Scale; BPSD: Behavioural and Psychological Symptoms in Dementia; CSF: Cerebrospinal Fluid; CNS: Central Nervous System; DA: Dopamine Agonist; FDG- PET: Fluorodeoxyglucose- Positron Emission Tomography; FRSSD: Functional Rating Scale for Symptoms in Dementia; FTD: Frontotemporal Dementia; GDS: Geriatric Depression Scale; LBD: Lewy Body Dementia; MCI: Mild Cognitive Impairment; MMSE: Mini Mental State Examination; MT: Music Therapy; NPI: Neuropsychiatric Inventory; OFC: Orbitofrontal Cortex; PDD: Parkinson's Dementia; PwD: Patients with Dementia; RCT: Randomized Controlled Trial; RT: Reminiscence Therapy; SSRI: Selective Serotonergic Reuptake Inhibitors; VaD: Vascular Dementia; VS: Ventral Striatum; VT: Validation Therapy

Introduction

Dementia is a disease of our brain that leads to cognitive disorders, functional decline, and behavioural changes. The most common type of dementia is Alzheimer's disease (AD), that affects more than 50 million people worldwide now, and this number is estimated to double every 20 years [1]. Behavioural and Psychological Symptoms in Dementia (BPSD) are important because they cause burden both to the patients and the caregivers, and most times lead to early institutionalization. Apathy is the most common BPSD and it is highly prevalent from early to late stages of dementia. It is also common in many different types of dementia, such as AD, frontotemporal dementia (FTD), Parkinson dementia (PDD) and vascular dementia (VAD). It has been found that 88% of patients with AD had BPSD, of which apathy reported to occur 27% to 72% of patients [2]. Various definitions have been used in order to identify apathy and it has been described as a symptom and as a syndrome. These definitions are described in detail below under the umbrella of criteria. Apathy is associated with greater caregiver distress and affects the patient's cognitive abilities. Sometimes it is under-diagnosed because it shares some common clinical features with depression [3].

The diagnostic criteria for apathy include diminished motivation in at least two of the three following domains: a) self-initiated or environment- stimulated behaviour, b) cognitive behaviour goal-directed (loss of ideas and curiosity) and c) emotional behaviour (loss of spontaneity and emotional responsiveness). In order to make a diagnosis of apathy the symptoms must persist for at least 4 weeks and be associated with functional decline [4]. Some of these clinical features can be: diminished interest, fatigue and lack of insight [3]. Hence, apathy has been associated with functional disability, self-neglect, reduced daily functioning, poor quality of life and caregiver distress [2].

The neuropathology of apathy in dementia has been studied in AD. It has been found that higher levels of apathy are associated to increased tangle burden, neuronal loss, and increased phospho-tau levels in the cerebrospinal fluid (CSF) [5]. Fluorodeoxyglucose-positron emission tomography (FDG-PET) studies have demonstrated that apathy in AD is associated with reduced metabolism in some temporal regions, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), ventral striatum (VS) and medial thalamus [6]. These findings are similar to studies with PDD patients [6]. Studies that used SPECT has demonstrated that reduced perfusion in ACC and OFC is associated with apathy in AD [6]. Nevertheless, it is crucial to mention that currently there is no understanding of how these neuropathology findings are linked to apathy. It is also unknown whether the effect is independent of general atrophy [7]. Furthermore, imaging studies report a connection between cholinergic, dopaminergic, serotonergic, and GABAergic neurotransmitters and apathy in AD.

The evaluation of the efficacy of the pharmacological treatments relies on some scales, such as the Apathy Evaluation Scale (AES) and Apathy Scale (AS). Neuropsychiatric Inventory (NPI) is a broadly used questionnaire, which assesses the severity and frequency of apathy and it is validated in patients with dementia (PwD).

The current pharmacological treatment of apathy includes Selective serotonergic reuptake inhibitors (SSRIs), which affect both the dopaminergic and serotonergic neurotransmission. Current literature report limited evidence that cholinesterases inhibitors, and possibly memantine, could be helpful to treat apathy [8]. Moreover, other pharmacological treatments for apathy include CNS stimulants, atypical anti-psychotics, apomorphine, amantadine, but without significant results [9].

Nevertheless, the side effects of the above drugs should be well-considered. Therefore, there is a strong need for non-pharmacological interventions in order to manage apathy. Until now there are studies with isolated non- pharmacological interventions.

Aim of the Study

The current study aims to find a combination of non-pharmacological interventions that can reduce apathy of patients and their caregivers' burden, as well.

Materials and Methods

Subjects

We included sixty (60) patients with dementia and apathy symptoms in the current study. The inclusion criteria were: a) patients with dementia, b) patients with apathy symptoms, c) healthy informal caregivers. For the diagnosis of apathy, the NPI questionnaire (questions and sub-questions of apathy) was applied. The participants were diagnosed with different types and stages of dementia. Specifically, the 61% of the patients suffered from AD, the 6.6% from VaD, the 4.9% from Lewy Body Dementia LBD, the 11.5% from PDD, the 1.6% from FTD and the 13.2% from Mild Cognitive Impairment (MCI) (Table 1). The 53.3% of the sample were females (N = 32). At the time of the trial all the patients had been diagnosed at the Neurology Departments of the General Hospitals of Thessaloniki and Athens. The caregivers have been informed and given written consent. We had approval of the Ethics Committee of Alzheimer Hellas (14/14-09-2013). There was no dropout rate.

	Mean (SD) or N (%)
Females, N (%)	32, (53.3%)
Age	73.8 (8.34)
Years of education	10.53 (4.5)
MMSE	19.85 (5.58)
ACE-R	56.63 (18.70)
GDS	7.38 (5.70)
FRSSD	17.42 (12.90)
NPI Results	8.20 (2.24)
NPI Distress	3.83 (0.92)

Table 1: Baseline characteristics of the sample.

Procedure

This is a cross-over randomized controlled trial. The NPI questions and sub-questions about apathy were applied to the family caregivers at the beginning of the process. The results were recorded and then the patients were randomly assigned into 6 different groups of 10 participants each. Every group received the same non-pharmacological interventions, but on a different sequence-order. The sequence of the interventions among groups is shown on table 2. Each intervention was taken place for five days, there was two days wash-out period and at the morning of the 6th day NPI questionnaire (only apathy questions and sub-questions) were applied again, in order to record the results.

Group	Sequence	1st week	2st week	3st week
1	ABC	A	B	C
2	ACB	A	C	B
3	BAC	B	A	C
4	BCA	B	C	A
5	CAB	C	A	B
6	CBA	C	B	A

Table 2: The sequence of the procedure (A= Body Exercise BE, B= Reminiscence Therapy RT, C= Music Therapy MT).

Interventions

The interventions were chosen based on three factors: a) they should be easily performed by the informal caregivers, b) they belonged in different categories; RT is a cognitive intervention, BE belongs to "other interventions" and MT is a sensory intervention, c) they are pleasurable and d) they have no known side-effects.

Body exercise

Studies have reported that 30 - 45' min of BE three times a week may have positive results on the BPSD [10,11]. A higher frequency of BE is related to better results. Our intervention was administrated every day, for 30min., five days, every morning after breakfast. All the family caregivers chose walking, as the easiest BE for their patients. The duration of the intervention has been chosen in accordance with the duration of most trials.

Reminiscence therapy (RT)

It is a person-centred approach that aims to arouse positive memories from the past to the PwD. It involves discussion of past happy moments and events of patient's life, using prompts to evoke memories or conversation. A large Cochrane review [12] for the BPSD in PwD mentions that the highest frequency was 60min a day for five days a week. The current study involved a 60min session every day for 5 days a week, every morning after breakfast. Photographs, videos and old letters have been used.

Music therapy (MT)

According to the large Cochrane review for BPSD in PwD it seems that most trials used 30 minutes of MT [13]. Also, this study had not apathy as a target. Owing to the heterogeneity of our sam-

ple (different types of dementia and stages) we resorted to only "listening to music" therapy. The preferable music of the patient was used daily for 45 minutes every morning after breakfast.

Measures

- **Mini mental state examination (MMSE)** [14,15]: MMSE is a 30-point questionnaire that is used to evaluate the global cognitive status. It is also used to estimate the severity of cognitive decline. This questionnaire examines registration, attention, recall, language and orientation. Higher scores indicate better cognitive performance and lower scores severe cognitive decline.
- **Addenbrooke's cognitive examination revised (ACE-R)** [16,17]: ACE-R is a 100-point questionnaire that is used to evaluate the global cognitive impairment. It includes MMSE. It is highly sensitive and can be used for the assessment of the severity of dementia. It includes questions about orientation, registration, attention, concentration, recall, verbal fluency, memory, language, spatial abilities, perceptual abilities and recognition. Higher scores indicate better cognitive performance.
- **Geriatric scale of depression (GDS)** [18,19]: This scale is a questionnaire of 30 questions examining whether the patient has depression. The patient answers with a YES/NO. Higher scores indicate higher level of depression.
- **Functional rating scale for symptoms in dementia (FRSSD)** [20,21]: It is a scale to access the Activities of Daily Living. The scale is a questionnaire which is completed by caregivers and includes 14 different daily activities, such as: eating, dressing, incontinence, speaking, sleeping, recognition of faces, personal hygiene, memory of names, memory of events, alertness, agitation, space orientation, emotional status, socialization**.** The scale is scored from 0 - 3 for each question (whereas 0= fully independence and 3= fully dependence). Higher scores indicate lower level of functionality (Activities of Daily Living).
- **Neuropsychiatric inventory (NPI)** [22,23]: The questionnaire is administered to the caregiver. It evaluates the frequency and severity of each symptom and the impact that apathy and other symptoms have on the caregiver burden. It is a valid and reliable tool, that has been translated into approximately 40 languages. It has been designed for different clinical trials and shows the behavioral symptoms in different neurodegenerative diseases [24]. It has been used in approximately 350 clinical trials and it is a useful measurement in order to evaluate the behavioral changes in AD and other dementias. Analytically, the questions of the NPI for apathy are:
  - Has the resident lost interest in the world around him/ her?
  - Does the resident fail to start conversation? (score only if conversation is possible)
  - Does the resident fail to show emotional reactions that would be expected (happiness over the visit of a friend or family member, interests in the news, sports, etc.)?
  - Has the resident lost interest in friends and family members?
  - Is the resident less enthusiastic about his/her usual interests?
  - Does the resident sit quietly without paying attention to things going on around him/her?
  - Does the resident show any other signs that he/she doesn't care about doing things?

The NPI questionnaire results in two scores; the first (NPI Result) is the result of the multiply of frequency and severity of the behaviour while the second (NPI Distress) is the impact (distress) that this behaviour has on the caregiver.

Data analysis

Categorical variables were presented as percentages while continuous variables were presented as Mean value and Standard Deviation (SD). Wilcoxon signed-rank test was used, because the distribution of the differences between the samples cannot be assumed to be normally distributed. Wilcoxon test applied to every group in order to find the combination of non-pharmacological interventions that was the most effective for apathy. Chi-square test was used in order to find differences among gender in the 6 groups and finally z value score was used in order to find the type of dementia in each group. P values less than 0.05 were considered statistically significant. SPSS 25.0 (IBM Inc., Armonk, NY) was used for the statistical analysis.

Results

Table 1 shows the baseline characteristics of the sample. The Mean scores of all the patients at baseline were: MMSE= 19.85 (SD = 5.5), ACE-R = 56.63 (SD = 18.7), GDS = 7.38 (SD = 5.7), FRSSD = 17.42 (SD = 12.9), NPI Results = 8.2 (SD = 2.2) and NPI Distress = 3.83 (SD = 0.9). The percentage of the different types of dementia of the sample is shown on table 3. The mean score of the age of the 6 groups was 73.8 (SD 2.71) years old. Chi-square was used for the evaluation of the gender. Pearson chi-square score was p = 0.224 for gender, which means there is no statistically significant difference among groups. Z test was used for the diagnosis of the sample: group 1 had a mean score of 3.40 (SD 3.68), group 2 had

2.60 (SD 2.98), group 3 had 3.60 (SD 3.59), group 4 had 3.10 (SD 3.69), group 5 had 2.60 (SD 2.87) and group 6 had 1.40 (SD 0.69) at baseline.

AD	VAD	LBD	PDD	FTD	MCI
61%	6.6%	4.9%	11.5%	1.6%	13.2%

Table 3: Percentages of the different types of dementia of the sample.

The results of the Wilcoxon test showed that the most effective combination of the above mentioned non-pharmacological interventions that can reduce apathy is: RT followed by BE, followed by MT. Group 3 received the three non-pharmacological interventions in the sequence: RT- BE- MT. Group 3 applied RT in the first week and had a statistically significant reduction on apathy (p = 0.007). During the second week BE was applied and it reduced apathy further (p = 0.013). In the third week MT was applied and had also a statistically significant reduction of apathy, as well (p = 0.027). The same combination reduced caregivers' distress, as well. RT in the first week reduced caregivers' burden (p = 0.006). BE in the second week reduced caregivers' distress further (p = 0.016) and finally in the third week, MT reduced also statistically significant the caregivers' burden, (p = 0.030). Group 3 included 5 participants with AD (50%), 2 participants with MCI (20%), 1 patient with DLB (10%) and 2 patients with PDD (20%). Group 3 included 5 males and 5 females participants. The average age of the participants in group 3 is 71.6 years old (SD 8.2). Table 4 shows the Wilcoxon results for all 6 different groups of PwD and caregivers, as well.

Group 1	**Baseline NPI**	**NPI before intervention A**	**A-B**	**B-C**
Mean Score ± SD	8 ± 2.52	8 ± 2.52 - 7 ± 2.35	7 ± 2.35 - 6 ± 1.26	6 ± 1.26 - 8 ± 2.60
Percentiles		6-9.75, 5.50-8	5.50-8, 4-6	4-6, 6-9.75
p		0.336	0.034	0.610
Group 2	**Baseline NPI**	**NPI before intervention A**	**A-C**	**C-B**
Mean Score ± SD	8 ± 2.07	8 ± 2.07 - 8 ± 2.34	8 ± 2.34 - 8 ± 2.11	8 ± 2.11 - 6 ± 1.34
Percentiles		7.50-9, 4-9	4-9, 6-8.25	6-8.25, 4-6
p		0.956	0.831	0.026
Group 3	**Baseline NPI**	**NPI before intervention B**	**B-A**	**A-C**
Mean Score ± SD	8 ± 2.66	8 ± 2.66 - 5 ± 1.84	5 ± 1.84 - 4 ± 1.63	4 ± 1.63 - 3 ± 0.69
Percentiles		7.50-12, 4-6.50	4-6.50, 2-4	2-, 2-2
p		0.007	0.013	0.027
Group 4	**Baseline NPI**	**NPI before intervention B**	**B-C**	**C-A**
Mean Score ± SD	8 ± 1.10	8 ± 1.10 - 5 ± 1.39	5 ± 1.39 - 8 ± 1.64	8 ± 1.64 - 6 ± 1.61
Percentiles		7.50-9, 4-6	4-6, 6-9	6-9, 6-8.25
p		0.007	0.910	0.037
Group 5	**Baseline NPI**	**NPI before intervention C**	**C-A**	**A-B**
Mean Score ± SD	8.5 ± 2.40	8.5 ± 2.40 - 8 ± 1.96	8 ± 1.96- 8 ± 1.94	8 ± 1.94, 6 ± 1.34
Percentiles		7-9, 5.50-9	5.50-9, 5.50-9	5.50-9, 4-6
p		0.803	1	0.028
Group 6	**Baseline NPI**	**NPI before intervention C**	**C-B**	**B-A**
Mean Score ± SD	8 ± 2.79	8 ± 2.79 - 8 ± 2.17	8 ± 2.17 - 5 ± 2	5 ± 2 - 8 ± 1.96
Percentiles		6-12, 6-8.25	6-8.25, 4-8	4-8, 5.50-9
p		0.862	0.030	0.942

Table 4: Results NPI (PwD).

Group 1	Baseline NPI	NPI before intervention A	A-B	B-C
Mean Score ± SD	4 ± 0.87	4 ± 0.87 - 4 ± 0.78	4 ± 0.78 - 3 ± 0.73	3 ± 0.73- 4 ± 0.78
Percentiles		3-5, 3-4.25	3-4.25, 2-3.25	2-3.25, 3-4.25
p		0.859	0.066	0.646
Group 2	**Baseline NPI**	**NPI before intervention A**	**A-C**	**C-B**
Mean Score ± SD	4.5 ± 1.10	4.5 ± 1.10 – 3.5 ± 1.05	3.5 ± 1.05 - 4 ± 1.10	4 ± 1.10 – 2 ± 0.67
Percentiles		3-5, 3-5	3-5, 3-5	3-5, 2-3
p		0.117	0.564	0.006
Group 3	**Baseline NPI**	**NPI before intervention B**	**B-A**	**A-C**
Mean Score ± SD	4 ± 0.87	4 ± 0.87 – 2 ± 0.48	2 ± 0.48 – 1.5 ± 0.82	1.5 ± 0.82 - 1 ± 0.78
Percentiles		3.75-4.25, 2-3	2-3, 2-2	2-2, 1-2
p		0.006	0.016	0.030
Group 4	**Baseline NPI**	**NPI before intervention B**	**B-C**	**C-A**
Mean Score ± SD	3.5 ± 0.96	3.5 ± 0.96 – 3 ± 0.69	3 ± 0.69 – 3 ± 0.84	3 ± 0.84 – 3.5 ± 0.84
Percentiles		3-4.25, 2-3	2-3,3-4	3-4, 3-4
p		0.041	0.630	0.755
Group 5	**Baseline NPI**	**NPI before intervention C**	**C-A**	**A-B**
Mean Score ± SD	3.5 ± 0.84	3.5 ± 0.84 - 3.5 ± 0.84	3.5 ± 0.84 - 3 ± 0.67	3 ± 0.67- 2.5 ± 0.69
Percentiles		3-4, 3-4	3-4, 3-4	3-4, 2-3
p		1	0.317	0.216
Group 6	**Baseline NPI**	**NPI before intervention C**	**C-B**	**B-A**
Mean Score ± SD	4 ± 0.94	4 ± 0.94 - 4 ± 0.99	4 ± 0.99 - 3 ± 1.03	3 ± 1.03- 3 ± 0.67
Percentiles		3.75-5, 3-5	3-5, 2-4	2-4. 3-4
p		1	0.027	0.972

Table 5: Results NPI (Caregivers' Distress).

Discussion and Conclusion

According to this study the most effective non-pharmacological combination for the symptom of apathy in PwD and their caregivers' burden is RT- BE-MT. It has not been found in recent literature a combination of non-pharmacological interventions that have reduced apathy, but also there are no studies with a non- pharmacological intervention with apathy as a target with the same design as in our study. RT has shown promising results for the management of several BPSD; however, the literature lacks trials that have focused on the reduction of apathy [12]. Amieva., *et al.* [25] conducted an RCT (parallel-group trial, with a two-year follow-up), with 326 participants for 90min once a week for 3 months and then once every 6 weeks for 21 months as a follow-up for the symptoms of apathy. The study did not find significant positive results after the follow-up [25]. Perhaps they had no results because the intervention was only once a week for the first three months and then once every 6 weeks for 21 months. Also, another possible explanation is that the duration of intervention in all this period was too small. In addition, there is another RCT with 61 patients where the RT intervention lasted 40 - 50 minutes once a week for 12 weeks [26]. The weakness of the current trial was a) the intervention was once a week and b) there was an absence of a control group [26]. The study included patients who had depression and apathy symptoms and found positive results, but not statistically significant for the apathy [26]. However, having the same sample for evaluating depression and apathy is a risk of bias and therefore the results of the trial remain ambivalent.

There is a crucial lack of evidence in the current literature about non- pharmacological interventions for apathy [27]. Lastly, a large

Cochrane Review for the efficacy of MT in apathy has been conducted but no positive results were mentioned [12]. Also, there are no significant results in apathy [28].

Our results showed that the most effective combination of non-pharmacological interventions for the reduction of apathy in PwD is also the most effective combination of non-pharmacological interventions for the reduction of the apathy distress of their caregiver. One possible explanation is that the caregivers' burden is directly in dependence with the behavior of PwD. Therefore, a non-pharmacological intervention that can control a strange behavior, it can be an effective solution for the reduction of the caregivers' burden, as well. Furthermore, RT when applied as a first treatment reduced statistically significant apathy (in both group 3 and 4). Therefore, it seems that a combination of cognitive intervention (RT)- BE and sensory intervention (MT) is the best one for the reduction of apathy in PwD and their caregivers. As we all know there are no studies with combinations of non-pharmacological interventions for PwD. This is the first study and there are many questions in this field. One potential question that should be examined in the future, is "can all the cognitive interventions reduce apathy, when applied first?". Therefore, there is a need for comparative studies.

RT seems to be an effective intervention. Nevertheless, future studies should examine what kind of memories should arise. Taking for granted that it would be best to arise positive memories from the past, it is risky, because with RT negative memories may also appear. In the current study, we decided to use only positive memories and not negative, in order to motivate our patients, and not to add depressive symptoms.

In conclusion, as apathy is one of the most common symptoms in all types and stages of dementia, it is urgent to find some practical and beneficial non-pharmacological interventions or combinations of them for its treatment. The caregivers' burden should be also well - considered. In addition, the current pharmacological treatments for the apathy, apart from the fact that have serious side-effects, do not actually treat apathy effectively. It is also crucial to diagnose apathy correctly because it sometimes may seem like depression. RT can have positive effects, when applied first, however further studies should use valid methodology and evaluation methods and conduct large RCT in order to establish safe conclusions. There is a strong need for further research, as most of the trials do not come to safe conclusions on the non-pharmacological interventions that can reduce apathy. In the future, it is urged to clarify what type of RT, BE, MT is more beneficial, the duration of each intervention, and if there are long-term benefits of the effective combination we used.

Finally, the strength of our study is its design, because it is a crossover RCT, in which PwD were randomly assigned in 6 groups and the interventions have been given to them randomly, as well. The sequence of the procedure does not interfere with the results. Risk of bias has been avoided. Furthermore, our results affect both genders, and different types and stages of dementia. There is a heterogeneity of our sample, nevertheless we aimed to find non-pharmacological solutions for every PwD. NPI is a valid and trustworthy tool, flexible and easy to use. Another strength of the study is the importance of its results. It is a matter of fact, that the caregivers spent more time with their patients, and this could be an explanation for our positive results. If this is the only explanation, we would wait that all the combinations could show beneficial effects. This underlines more the importance of our results. The limitations of the study are: a) the short period that the interventions lasted (however, caregivers need rapid solutions), b) the interventions were administered by the caregivers (however, they were fully informed and they could ask for guidelines anytime), and c) there was no follow-up.

Conflict of Interest

The authors declare that there is no conflict of interest.

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