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Efficacy of Doll thErapy compared with standard treatment in the control of behavioral and psychologic Symptoms and CaReglver Burden in dEmentia: DESCRIBE a randomized, controlled study

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ABSTRACT

Behavioral and psychologic symptoms of dementia (BPSD) are frequent and represent a burden for patients and caregivers; in particular, the presence of agitation and aggression (A/A) has an important impact on patients' quality of life. As psychotropic drugs can induce severe collateral effects, the use of a first line non-pharmacologic approach is highly recommended.

Here we evaluate the effect of doll therapy (DT) on A/A in geriatric patients with moderate to severe dementia hospitalized in an acute geriatric unit.

We enrolled fifty-two acute in-patients with dementia and A/A. Subjects were randomized to DT (26) or standard treatment (ST, 26), we measured agitation and caregiver burden with standard clinical scales at baseline and during treatment. In order to evaluate the effect of DT withdrawal, we carried out a telephonic follow-up interview after 1 and 4 weeks from hospital discharge.

DT is more effective than ST in the control of agitation, but not in reducing the professional caregiver burden. The use of pro re nata psychotropic drugs was reduced in patients treated with DT. After DT withdrawal, A/A progressively increased.

In conclusion we show that DT may be more effective than ST in the control of A/A in acute geriatric in-patients affected by dementia. Our results suggest that, in patients affected by severe to moderate forms of dementia with A/A, DT may be used as a first line treatment, not only in nursing home residents, but also in acute care geriatric in-patients.

Keywords: dementia; behavioral and psychologic symptoms in dementia; hospital; doll therapy; non-pharmacological approach.

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Introduction

In 2018 about 50 million people in the world lived with dementia[1], as age is an important risk factor for the development of dementia, the number of patients affected by this disease is expected to significantly rise within the next years. According with the World Alzheimer Report of 2018 the number of persons with dementia will increase until 152 million in 2050[1]. The burden of dementia on health and social care systems is enormous, the total estimated worldwide cost due to the disease is about a trillion US dollars/year, and this number is forecasted to double by 2030[2]. Beyond the financial impact, there is the emotional burden of the disease: the unstoppable progression of the patient toward the loss of communication abilities, the loss of independency and the development of behavioral and psychologic symptoms of dementia (BPSD) represents a huge emotional stress and an important burden for the caregivers. BPSD includes agitation, elation, wandering, depression, delusions and hallucinations[3], affects more than 80% of persons living with dementia[4–6] and often presents in clusters[7]. BPSD will appear in about 20% of initially asymptomatic patients within two years from the diagnosis, however almost the 100% of patients with dementia will present BPSD at a certain point of their disease[8–10]. Amongst BPSD the presence of agitation and aggression (A/A) severely affects patients' and caregivers' quality of life[11,12], increases disability with earlier institutionalization[13] worsens with the disease progression [14] and is associated with higher health care costs[15].

Although pharmacologic treatment is commonly utilized for treating A/A, this approach is often insufficient to control the symptoms[16]. Drugs may cause severe adverse events as extrapyramidal symptoms, somnolence, sedation, fatigue, risk of falls, appetite and weight gain, urinary incontinence, cardio-vascular effects and cerebrovascular accidents [17] may increase mortality [18] and may also worsen cognitive performances [19]. Hence a non-pharmacologic approach is considered as a valid alternative to pharmacologic[20,21] and it is strongly recommended as a first line treatment for BPSD by the American Association for Geriatric Psychiatry[22].

Non-pharmacologic approach include different interventions: cognitive/ emotion-oriented inter-ventions, that aim to improve emotional and social function of patients with dementia, this approach includes reminiscence therapy, valida-tion therapy and orientation to reality[23]. Sensory and multi-sensory stimulation interventions that aim to increase alertness and reduce agitation as art therapy, aromatherapy, music therapy, and others[24]. Psychological interventions that aim to ameliorate BPSD as behavior management, animal-assisted therapy and others, see for a systematic review[21]. Amongst different non-pharmacologic approaches the doll therapy (DT) has been extensively studied, see[25] for a comprehensive review.

The mechanism of action of DT is not completely understood, the attachment theory has been evoked to explain the effect of DT in the management of BPSD in patients living with dementia[26,27]. Attachment theory was first developed by John Bowlby mainly to explain the behavior of abandoned children; however, it has been further adapted to explain aging and dementia[26,28,29] Attachment refers to the emotional connection with a particular person; the subject develops feelings of protection and needs of care towards the loved one. Some of the behaviors described as BPDS as wandering, repetitive questioning, crying, agitation and even aggressiveness in individuals with dementia

might be interpreted as attachment requests. During BPSD, DT may catalyze patients' attention and concentrate their requests and their emotions on the doll, that becomes a transitional object and, sometimes, is considered as a real baby needing care[30]. The attachment developed to the doll, brings the patient back to his/her past experiences as a person able to care for others instead of needing care[26,27,31]. Moreover, taking care of the doll may increase patients' self-esteem[32], create therapeutic alliance bond[25], and help the patients to communicate with the environment and the caregivers [26,32,33]. Thus, DT may be a promising tool in the non-pharmacologic approach of BPSD in dementia.

Until now DT has been mainly evaluated in nursing homes, reviewed in[25,31], overall the studies reported an amelioration of BPSD, with improvement of wellbeing, reduction of the use of antipsychotic drugs[34]and increase in the therapeutic alliance between the patients and the professional caregivers[25,35]. However the majority of the studies on DT were cohort, case-control and observational studies[25]. The efficacy of DT was assessed only in long-term care facilities and not in acute geriatric in-patients, thus we designed this study in order to evaluate the efficacy of DT in patients with dementia and A/A in an acute geriatric unit with a randomized controlled approach.

Methods

Study design

DESCRIBE is a randomized controlled trial with two parallel arms, developed in order to assess the efficacy of DT compared with Standard Treatment (ST) in the control of A/A and in relieving the caregiver burden in persons with dementia hospitalized in an acute geriatric unit. The study follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines for non-pharmacologic treatments[36].

Participants

To evaluate the role of DT in acute patients we enrolled acute geriatric in-patients hospitalized in the Geriatric and Bone Diseases Unit of the City of Health and Science Hospital in Torino (TO) between the 1 January 2019 and 31 October 2019 according with the following inclusion/exclusion criteria.

Inclusion criteria: age ≥65 years; diagnosis of dementia moderate to severe Clinical Dementia Rating scale (CDR) ≥2; presence of agitation and/or aggressiveness; manual and visual abilities sufficient in order to interact with the doll.

Exclusion criteria: age <65 years; refuse to participate; mild forms of dementia (CDR<2); contrainication for DT as experience of mournful or traumatic events related to parental experience; life expectancy lower than 3 months; infectious diseases requiring isolation; negative interaction with the doll.

Patients were randomly assigned at doll therapy (DT) or standard treatment (ST), the randomization was carried out by computer-generated tables to allocate treatments: the patients received a consecutive number after enrolment and were subsequently allocated to randomization list, according with[37]. The PI generated the randomization list.

Intervention

The doll used in the study is the "empathy doll"; these dolls are designed to obtain an optimal interaction with patients and to arouse empathy (Fig. 1).

Nurses responsible for doll administration received detailed information on the aim of the study and on the role of DT in controlling A/A. An expert neuropsychologist was responsible to train nursing staff in the doll administration and in the observation of patients' interaction with the

doll. The researchers informed patients' caregivers on the aim and the efficacy of DT by a one-to-one discussion, at the end of the discussion an informative brochure was released. In order to evaluate the patients interaction with the doll we used the Engagement Observation Rating Tool for Doll Therapy [35,38]. Patients with positive attitude (good attention and attitude and appropriate interaction with doll) and neutral attitude (ignore the doll) towards the doll were included in the study and immediately randomized to DT or standard treatment (ST). Patients with negative interaction (refuse the doll, become agitated and or aggressive) were excluded from the study.

Figure 1. Empathy dolls. The pictures show the dolls used in the study (panel A), interaction between patient and doll (panel B).

The trained nurse introduced the doll to the patient as gift: "good morning Mr/Mrs look! This is for you!", and left the doll in his/her room such as it can be easily accessible; the researcher observe the patient interaction with doll for 5 minutes after administration and 5 minutes before the end of administration. Interaction between patients and doll was noted in the Observation Rating Tool for Doll Therapy. Nurses interacted with patient and doll at administration and withdrawal; otherwise, the patient was allowed to freely interact with the doll. If the patient refuse the doll, the caregiver would not insist.

In DT group the doll were administered two times a day for two hours in the morning, two hours in the afternoon and in case of agitation/ aggressiveness. The administration of DT was the treatment first choice; if the agitation/ aggressiveness persist, the use of pharmacologic treatment was allowed and noted. In the control group, the caring physician was allowed to choose the psychotropic drugs, according with standard clinical care (ST). For the pro re nata (PRN) psychoropic drug administration in case of A/A, haloperidol was used as first line treatment, promazin as second line. DT and controls were comparable for used for the control of BPSD at baseline (Table 1).

In order to evaluate the effect of discontinuation of DT, we carried out a follow-up by telephonic interviews after 1 and 4 weeks from hospital discharge; whilst DT was stopped, antipsychotic drugs treatment was continued. Figure 2 shows the study flow chart.

Table 1. Treatment used for the control of BPSD at baseline according to randomization. Percentage and confidence of intervals (CI) are shown.

	DT (26)	ST (26)
Quetiapine (%)	30.8 (17-50)	27 (14-46)
Haloperidol (%)	19.2 (9-38)	19 (9-38)
Promazin (%)	7.7 (1.4-24)	7.7 (1.4-24)
Trazodon (%)	15.4 (6-34)	12 (4-29)
Benzodiazepine (%)	4 (0.2-19)	4 (0.2-19)
More than 1 drug (%)	4 (0.2-19)	7.7 (1.4-24)
No drug (%)	0 (0-13)	0 (0-13)

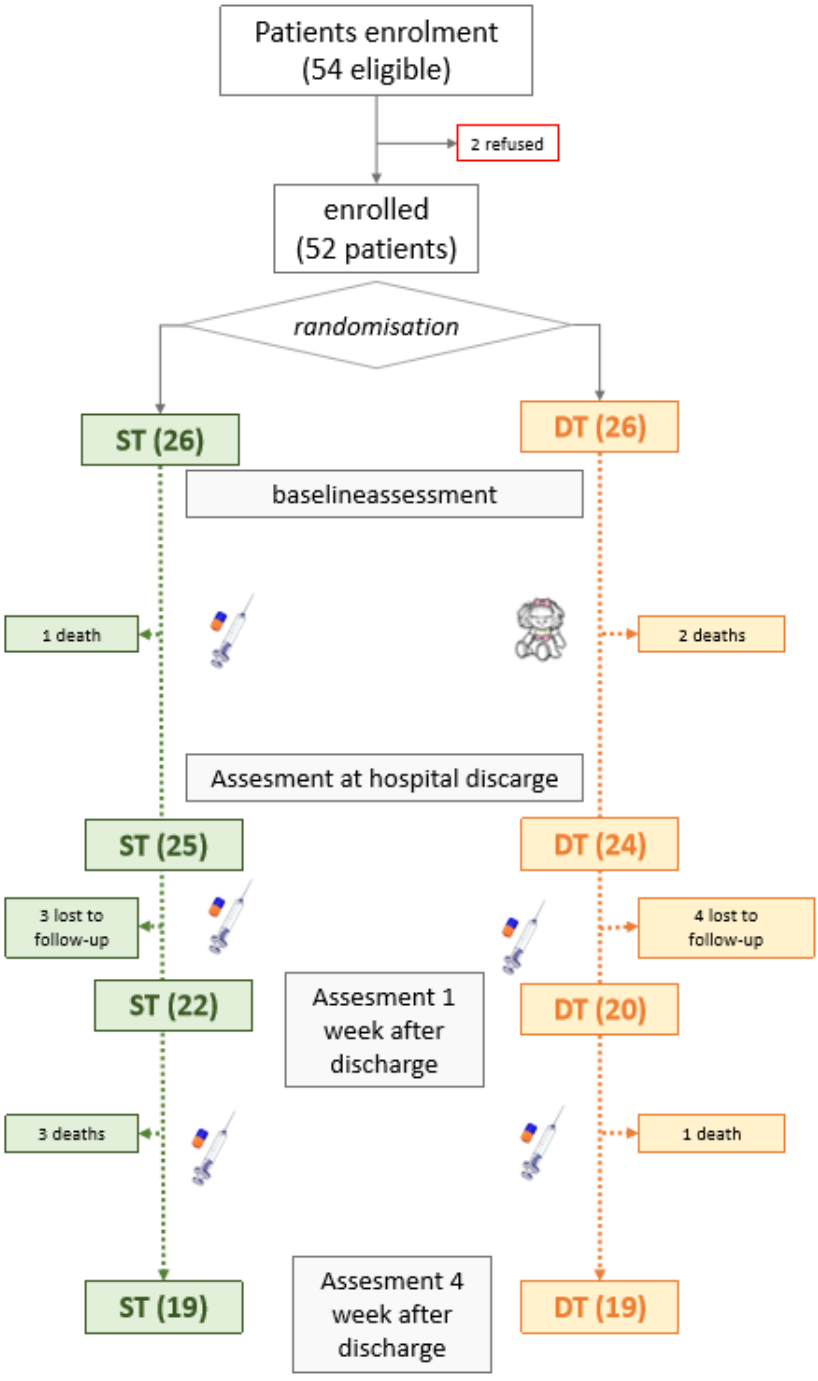

Figure 2. Study flow chart. The diagram shows the study design with the number of patients at each visit.

Outcomes

Primary outcomes were the effect of DT on A/A and on professional caregiver burden

Secondary outcome was the effect of DT on family caregiver burden.

Analyzed variables

Presence of A/A was evaluated with the A.Di.Co scale, this is a scale derived from the DISCO scale[14,40].The A.Di.Co evaluate the presence of BPSD using 10 items dived in clusters.

The scores is zero if there are no BSPD, 1 if there is the patient is anxious or verbally aggressive or has hallucination (mild agitation), 2 correspond to the presence of moderate to severe agitation (A/A), the patient is agitated, physically aggressive or defensive.

In order to evaluate the professional caregiver burden we used the Gruetzner scale[41];the family caregiver burden was evaluated by the Caregiver Burden Inventory (CBI) scale[42],the presence of delirium was evaluated by the use of the Assessment test for delirium and cognitive impairment (4AT)[43]. Cognition and functional status were evaluated by the Short Portable Mental Questionnaire (SPMQ)[44],he Activity of Daily Living (ADL) scale and the Instrumental Activity of Daily Living (IADL) score[45] respectively.

Age, gender, length of hospital stays, and type of hospital discharge were also recorded. Data collection and analyses were blinded as respect to patients' treatment.

Variables of interest were collected at baseline, at hospital discharge and after 1 and 4 weeks from hospital discharge by telephonic interviews (Fig. 2).

Statistical analyses

As no previous studies measured the efficacy of DT in different setting using A.Di.CO the power analysis was conducted using an estimated large effect size (f = 0.40), an alpha level of 0.05, and a power of 0.8. A sample size of 52 is necessary (26 each group) for primary outcomes[46].

All the analyzed variables were tested for normality by the kurtosis test and they were all normally distributed. Patients randomized to DT were compared to patients randomized to ST by one-way ANOVA for continuous variables and by χ^2 test for gender. The effect of DT was evaluated per protocol using the two-way ANOVA for repeated measurements.

The PRN antipsychotic drugs administration was normalized for the length of hospital stay (number of PRN administration/length of hospital stay) and compared amongst the two groups by means of the Student's T-test for unpaired values. SPSS 25.0 were used for the statistical analyses and $p<0.05$ was considered statistically significant. Graphs were drawn using GraphPad 8.0 for Windows.

Ethical considerations

The Ethical Committee "Comitato Etico Interaziendale AO Città della Salute e della Scienza di Torino" approved the study (Ref. no. CE il 04/10/2018 protocol number 0098548).

Results

Fifty-four patients were eligible to the study, of those, 52 were enrolled, as two refused to participate. All the enrolled patients had a positive interaction with the doll (Fig.2).

DT is effective in reducing agitation and aggressiveness in acute geriatric in-patients.

The DT group did not significantly differ from patients in ST group for age, gender, cognition, level of independence, presence of delirium, duration of in hospital stay presence of A/A, professional and family caregiver burden (Table 2). The mean length of hospital stay was 10±1 days without statistical differences between the two treatment groups. During hospitalization three patient died, one in the ST and two in the

DT group. At discharge, DT was withdrawn in all the patients, except for one patient who wished to continue the treatment and has been considered lost at follow-up. After the first week, six patients were lost at follow up as it was impossible to reach them by phone, at the end of follow-up four patients were dead (Fig.2).

Table 2. General characteristics of patients according with treatment. Mean ± SE are shown, p values were calculated by one-way ANOVA and by χ2 test for gender. CBI: Caregiver Burden Inventory 4AT: Assessment test for delirium and cognitive impairment ADL: Activity of Daily Living IADL: Instrumental Activity of Daily Living SPMQ: Short Portable Mental Questionnaire CDR: Clinical Dementia Rating scale

	DT (26)	ST (26)	p value
Age (years)	87±5	84±7	0.078
A.Di.Co (score)	1.8±0.4	1.9±0.5	0.652
Greutzner (score)	18.4±10.5	22.9±13	0.208
CBI (score)	48.6±16.5	47.1±16.7	0.780
4AT (score)	6.1±3.3	6.7±3.5	0.603
ADL (score)	4.1±1.9	3.8±1.9	0.595
IADL (score)	2.5±3.0	3.8±1.9	0.495
SPMQ (score)	6.8±2.5	7.7±2.4	0.227
CDR (score)	2.6±0.7	2.9±0.5	0.180
Women (%)	68%	65%	0.433
Men (%)	32%	35%	

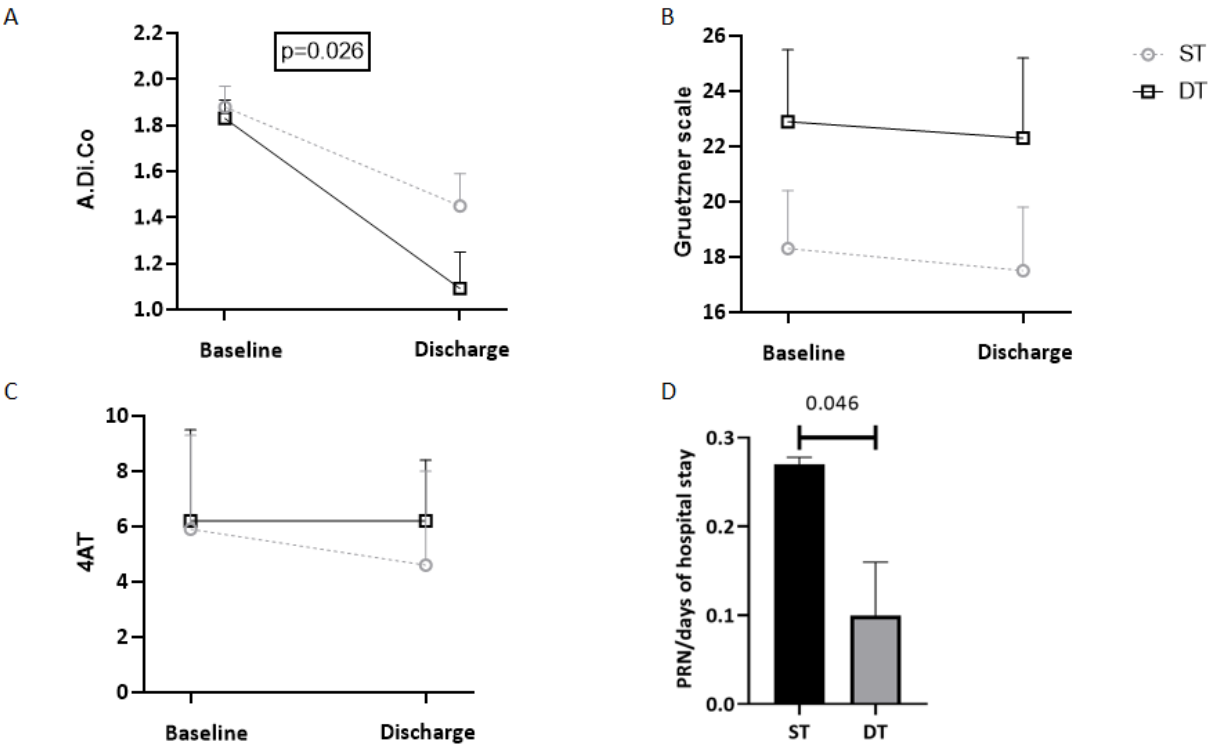

Figure 3. Effect of doll therapy in acute geriatric patients. Effect of DT versus ST on the ontrol of BPSD measures as A.Di.CO (panel A). Effect of DT versus ST in relieving the professional caregiver measured by the Gruetzner scale (panel B) and the family caregiver urden (C.B.I, panel C). Effect of DT versus ST in reducing the risk of delirium measured by 4AT (panel C). Effect of DT versus ST on the administration of PRN (panel D). Results of two-way ANOVA for repeated measurements are shown in box, significant differences versus aseline are shown by *. P values for PRN were compared by Student's T test.

DT was more effective in reducing A/A during hospital stay as respect to ST (Fig.3A), DT and ST were both ineffective in relieving the perceived professional caregiver burden (Fig. 3B) and in reducing the incidence of delirium (Fig. 3C). As regards pharmacologic treatment, the use of PRN was significantly lower in the DT group (Fig. 3D). In details, PRN administration was necessary in ≤2 times in 3 patients (11.5%) and more than 2 times during hospitalization in 2 patients (7.7%) in DT group; whereas in the ST group 13 patients (50%) needs PRN, of those 7 (27%) received more than 2 doses.

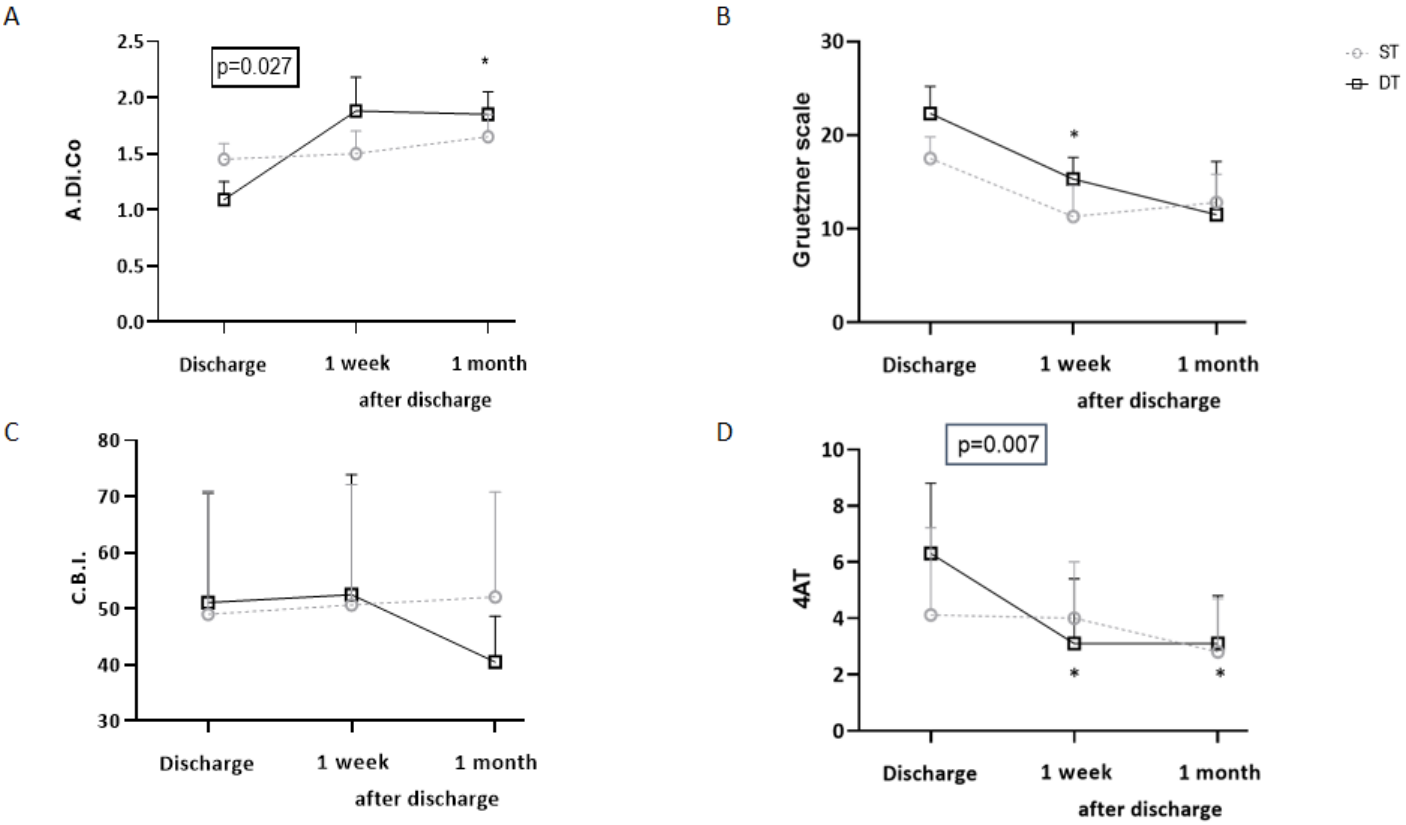

Figure 4. Effect of interruption of doll therapy in patients discharged from hospital. Effect of interruption of DT versus ST on the control of BPSD measures as A.Di.CO (panel A). Effect f interruption of DT versus ST on the professional caregiver measured by the Gruetzner scale (panel B) and the family caregiver burden (C.B.I, panel C). Effect of interruption of DT versus ST in reducing the risk of delirium measured by 4AT (panel D). Results of two-way NOVA for repeated measurements are shown in box, significant differences versus baseline are shown by *.

In order to evaluate the effect of DT withdrawal, all the patients were followed up for one month after hospital discharge with two telephonic interviews after 1 and 4 weeks.

During follow up we observed an increase in A/A, that was significantly higher in patients previously treated with DT (Fig.4A), there were no significant change in the professional (Fig.4B) and familiar (Fig.4C) caregiver burden. The Greutzner scale was evaluated at follow-up in patients discharged in nursing homes or long-term care units (22), whereas in patients returning home (20) only the C.B.I was evaluated. We observed a significant decrease in the incidence of the delirium regardless to previous treatment (Fig. 4D).

Discussion

Non-pharmacologic approach is highly recommended for patients with dementia and BPSD[22];amongst non-pharmacologic treatment the use of doll therapy has been shown as effective in the control of agitation and aggressiveness in patients affected by severe forms of dementia (reviewed in [25]). Despite general positive findings due to the type of intervention, a standardized approach is difficult to reach, there have been some attempt towards standardization of DT with well-designed randomized controlled clinical trials[47–50],the results of these trials agree on the efficacy of DT in ameliorating BPSD in nursing home residents. As regards acute hospital setting, this is the first attempt to evaluate the efficacy of DT with a randomized controlled approach.

This topic is of particular relevance as persons living with dementia are frequently hospitalized[51,52] and hospitalization heavily contributes to the increase of frequency and magnitude of BPSD[53,54] causing distress for both families[55] and professional caregivers[54]. Pharmacologic treatments used to control A/A are often burdened by severe collateral effects that may prolong hospital stay and increase the risk of in-hospital mortality[56], whereas non-pharmacologic approaches have less collateral effects[20,21].

DESCRIBE shows that, despite the short period of intervention, DT is effective in reducing A/A and in reducing the administration of PRN psychotropic drugs in an acute hospital setting. Reduction of psychotropic PRN may reduce collateral effects due to psychotropic administration and ameliorate clinical outcomes [16]. After DT withdrawal, we observed a progressive increase in A/A, despite hospital discharge. Even if these data may further support the role of DT in reducing agitation and aggressiveness, a certain caution in their interpretation is due as, we do not have data on potentially confounding factors as changes in the patients' psychosocial needs and in social interaction after hospital stay.

Despite the reduction of A/A we did not find a reduction in the professional caregiver burden, this may be due to the different components of the burden detected by the Gruetzner scale. In f-act, patients' agitation and aggressiveness is dir-ectly evaluated in only one item of the scale.

There are still some barriers in the application of DT, in fact some concerns about its extensive use have been raised: caregivers may be concerned by feelings of "infantilizing" the patient[57] and disputes between owners and non-owners of a doll have been reported. Furthermore, in some patients' dolls may lead to discomfort and distress [32], hence before starting DT it is important to evaluate the patient's attitude toward the doll. In our study, none of the caregivers, after adequate information, raised concerns about the use of dolls as first-line treatment in controlling patient's agitation/ aggressiveness, furthermore we did not observed disputes between owners and non-owners of a dolls even though the interaction between patients was not standardized and noted. A qualitative revision of clinical dossiers shows no disputes because of the doll. We do not observe negative interaction with the doll; it was generally well accepted and perceived as a gift.

As major limitation of our study, we acknowledged the lack of homogeneity in psychotropic drugs used; however, due to different clinical manifestation of patients with dementia it is almost impossible to standardize the treatment. Nevertheless, patients randomized to DT and ST were treated with similar drugs, thus reducing the bias. Moreover,

comparing DT with common clinical practice allow us to generalize our findings.

Before introduction of DT it is important to evaluate the patients' interaction with the doll, to have specific trained personnel and to discuss the treatment with the patient and the family. Patients with negative attitude towards the doll must not be treated with DT in order to avoid possible secondary effects as increased agitation and aggressiveness. The need for specific trained personnel may reduce the utilization of DT in acute hospital units; therefore, specific studies to clarify the cost effectiveness of this intervention may be useful to support the use of DT in the everyday clinical practice.

In conclusion, DT may be an option for the treatment of A/A also in acute care hospital units in patients with moderate to severe dementia as first line treatment.

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Conflict of interest: the Authors declare that there is no conflict of interest.

Data availability: the datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations list

Behavioral and psychologic symptoms of dementia: BPSD

Agitation and aggression: A/A

Doll therapy: DT

Standard treatment: ST

Caregiver Burden Inventory: CBI

Assessment test for delirium and cognitive impairment: 4AT

Short Portable Mental Questionnaire: SPMQ

Activity of Daily Living: ADL

Instrumental Activity of Daily Living: IADL

References

[1] 2018 Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia* **2018**, *14* (3), 367–429. https://doi.org/10.1016/j.jalz.2018.02.001.

[2] Prince, M. J. World Alzheimer Report 2015: The Global Impact of Dementia https://www.alz.co.uk/research/world-report-2015 (accessed Mar 5, 2020).

[3] Kales, H. C.; Gitlin, L. N.; Lyketsos, C. G. Assessment and Management of Behavioral and Psychological Symptoms of Dementia. *BMJ* **2015**, *350*, h369. https://doi.org/10.1136/bmj.h369.

[4] Lyketsos, C. G.; Carrillo, M. C.; Ryan, J. M.; Khachaturian, A. S.; Trzepacz, P.; Amatniek, J.; Cedarbaum, J.; Brashear, R.; Miller, D. S. Neuropsychiatric Symptoms in Alzheimer's Disease. *Izheimers Dement* **2011**, *7* (5), 532–539. https://doi.org/10.1016/j.jalz.2011.05.2410.

[5] Geda, Y. E.; Schneider, L. S.; Gitlin, L. N.; Miller, D. S.; Smith, G. S.; Bell, J.; Evans, J.; Lee, M.; Porsteinsson, A.; Lanctôt, K. L.; Rosenberg, P. B.; Sultzer, D. L.; Francis, P. T.; Brodaty, H.; Padala, P. P.; Onyike, C. U.; Ortiz, L. A.; Ancoli-Israel, S.; Bliwise, D. L.; Martin, J. L.; Vitiello, M. V.; Yaffe, K.; Zee, P. C.; Herrmann, N.; Sweet, R. A.; Ballard, C.; Khin, N. A.; Alfaro, C.; Murray, P. S.; Schultz, S.; Lyketsos, C. G.; Neuropsychiatric Syndromes Professional Interest Area of ISTAART. Neuropsychiatric Symptoms in Alzheimer's Disease: Past Progress and Anticipation of the Future. *Alzheimers Dement* **2013**, *9* (5), 602–608. https://doi.org/10.1016/j.jalz.2012.12.001.

[6] Ismail, Z.; Smith, E. E.; Geda, Y.; Sultzer, D.; Brodaty, H.; Smith, G.; Agüera-Ortiz, L.; Sweet, R.; Miller, D.; Lyketsos, C. G.; ISTAART Neuropsychiatric Symptoms Professional Interest Area. Neuropsychiatric Symptoms as Early Manifestations of Emergent Dementia:

Provisional Diagnostic Criteria for Mild Behavioral Impairment. *Alzheimers Dement* **2016**, *12* (2), 195–202. https://doi.org/10.1016/j.jalz.2015.05.017.

[7] Petrovic, M.; Hurt, C.; Collins, D.; Burns, A.; Camus, V.; Liperoti, R.; Marriott, A.; Nobili, F.; Robert, P.; Tsolaki, M.; Vellas, B.; Verhey, F.; Byrne, E. J. Clustering of Behavioural and Psychological Symptoms in Dementia (BPSD): A European Alzheimer's Disease Consortium (EADC) Study. *Acta Clin Belg* **2007**, *62* (6), 426–432. https://doi.org/10.1179/acb.2007.062.

[8] Savva, G. M.; Zaccai, J.; Matthews, F. E.; Davidson, J. E.; McKeith, I.; Brayne, C.; Medical Research Council Cognitive Function and Ageing Study. Prevalence, Correlates and Course of Behavioural and Psychological Symptoms of Dementia in the Population. *Br J Psychiatry* **2009**, *194* (3), 212–219. https://doi.org/10.1192/bjp.bp.108.049619.

[9] Hendriks, S. A.; Smalbrugge, M.; Galindo-Garre, F.; Hertogh, C. M. P. M.; van der Steen, J. T. From Admission to Death: Prevalence and Course of Pain, Agitation, and Shortness of Breath, and Treatment of These Symptoms in Nursing Home Residents with Dementia. *J Am Med Dir Assoc* **2015**, *16* (6), 475–481. https://doi.org/10.1016/j.jamda.2014.12.016.

[10] Ryu, S.-H.; Katona, C.; Rive, B.; Livingston, G. Persistence of and Changes in Neuropsychiatric Symptoms in Alzheimer Disease over 6 Months: The LASER-AD Study. *Am J Geriatr Psychiatry* **2005**, *13* (11), 976–983. https://doi.org/10.1176/appi.ajgp.13.11.976.

[11] Chiao, C.-Y.; Wu, H.-S.; Hsiao, C.-Y. Caregiver Burden for Informal Caregivers of Patients with Dementia: A Systematic Review. *Int Nurs Rev* **2015**, *62* (3), 340–350. https://doi.org/10.1111/inr.12194.

[12] Wetzels, R. B.; Zuidema, S. U.; de Jonghe, J. F. M.; Verhey, F. R. J.; Koopmans, R. T. C. M. Determinants of Quality of Life in Nursing Home Residents with Dementia. *Dement Geriatr Cogn Disord* **2010**, *29* (3), 189–197. https://doi.org/10.1159/000280437.

[13] Okura, T.; Plassman, B. L.; Steffens, D. C.; Llewellyn, D. J.; Potter, G. G.; Langa, K. M. Neuropsychiatric Symptoms and the Risk of Institutionalization and Death: The Aging, Demographics, and Memory Study. *J Am Geriatr Soc* **2011**, *59* (3), 473–481. https://doi.org/10.1111/j.1532-5415.2011.03314.x.

[14] De Mauleon, A.; Delrieu, J.; Cantet, C.; Vellas, B.; Andrieu, S.; Rosenberg, P. B.; Lyketsos, C. G.; Soto Martin, M. Longitudinal Course of Agitation and Aggression in Patients with Alzheimer's Disease in a Cohort Study: Methods, Baseline and Longitudinal Results of the A3C Study. *J Prev Alzheimers Dis* **2021**, *8* (2), 199–209. https://doi.org/10.14283/jpad.2020.66.

[15] Costa, N.; Wübker, A.; De Mauléon, A.; Zwakhalen, S. M. G.; Challis, D.; Leino-Kilpi, H.; Hallberg, I. R.; Stephan, A.; Zabalegui, A.; Saks, K.; Molinier, L.; Wimo, A.; Vellas, B.; Sauerland, D.; Binot, I.; Soto, M. E.; RightTimePlaceCare consortium. Costs of Care of Agitation Associated With Dementia in 8 European Countries: Results From the RightTimePlaceCare Study. *J Am Med Dir Assoc* **2018**, *19* (1), 95.e1-95.e10. https://doi.org/10.1016/j.jamda.2017.10.013.

[16] Howard, R.; McShane, R.; Lindesay, J.; Ritchie, C.; Baldwin, A.; Barber, R.; Burns, A.; Dening, T.; Findlay, D.; Holmes, C.; Hughes, A.; Jacoby, R.; Jones, R.; Jones, R.; McKeith, I.; Macharouthu, A.; O'Brien, J.; Passmore, P.; Sheehan, B.; Juszczak, E.; Katona, C.; Hills, R.; Knapp, M.; Ballard, C.; Brown, R.; Banerjee, S.; Onions, C.; Griffin, M.; Adams, J.; Gray, R.; Johnson, T.;

Bentham, P.; Phillips, P. Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease. *N. Engl. J. Med.* **2012**, *366* (10), 893–903. https://doi.org/10.1056/NEJMoa1106668.

[17] Tampi, R. R.; Tampi, D. J.; Balachandran, S.; Srinivasan, S. Antipsychotic Use in Dementia: A Systematic Review of Benefits and Risks from Meta-Analyses. *Ther Adv Chronic Dis* **2016**, *7* (5), 229–245. https://doi.org/10.1177/2040622316658463.

[18] Maher, A. R.; Maglione, M.; Bagley, S.; Suttorp, M.; Hu, J.-H.; Ewing, B.; Wang, Z.; Timmer, M.; Sultzer, D.; Shekelle, P. G. Efficacy and Comp arative Effectiveness of Atypical Antipsychotic Medications for Off-Label Uses in Adults: A Systematic Review and Meta-Analysis. *JAMA* **2011**, *306* (12), 1359–1369. https://doi.org/10.1001/jama.2011.1360.

[19] Bierman, E. J. M.; Comijs, H. C.; Gundy, C. M.; Sonnenberg, C.; Jonker, C.; Beekman, A. T. F. The Effect of Chronic Benzodiazepine Use on Cognitive Functioning in Older Persons: Good, Bad or Indifferent? *Int J Geriatr Psychiatry* **2007**, *22* (12), 1194–1200. https://doi.org/10.1002/gps.1811.

[20] Seitz, D. P.; Brisbin, S.; Herrmann, N.; Rapoport, M. J.; Wilson, K.; Gill, S. S.; Rines, J.; Le Clair, K.; Conn, D. Efficacy and Feasibility of Nonpharmacological Interventions for Neuropsychiatric Symptoms of Dementia in Long Term Care: A Systematic Review. *J Am Med Dir Assoc* **2012**, *13* (6), 503-506.e2. https://doi.org/10.1016/j.jamda.2011.12.059.

[21] Abraha, I.; Rimland, J. M.; Trotta, F. M.; Dell'Aquila, G.; Cruz-Jentoft, A.; Petrovic, M.; Gudmundsson, A.; Soiza, R.; O'Mahony, D.; Guaita, A.; Cherubini, A. Systematic Review of Systematic Reviews of Non-Pharmacological Interventions to Treat Behavioural Disturbances in Older Patients with Dementia. The SENATOR-OnTop Series. *BMJ Open* **2017**, *7* (3). https://doi.org/10.1136/bmjopen-2016-012759.

[22] Lyketsos, C. G.; Colenda, C. C.; Beck, C.; Blank, K.; Doraiswamy, M. P.; Kalunian, D. A.; Yaffe, K.; Task Force of American Association for Geriatric Psychiatry. Position Statement of the American Association for Geriatric Psychiatry Regarding Principles of Care for Patients with Dementia Resulting from Alzheimer Disease. *Am J Geriatr Psychiatry* **2006**, *14* (7), 561–572. https://doi.org/10.1097/01.JGP.0000221334.65330.55.

[23] Finnema, E.; Dröes, R. M.; Ribbe, M.; Van Tilburg, W. The Effects of Emotion-Oriented Approaches in the Care for Persons Suffering from Dementia: A Review of the Literature. *Int J Geriatr Psychiatry* **2000**, *15* (2), 141–161. https://doi.org/10.1002/(sici)1099-1166(200002)15:2<141::aid-gps92>3.0.co;2-5.

[24] Mileski, M.; Baar Topinka, J.; Brooks, M.; Lonidier, C.; Linker, K.; Vander Veen, K. Sensory and Memory Stimulation as a Means to Care for Individuals with Dementia in Long-Term Care Facilities. *Clin Interv Aging* **2018**, *13*, 967–974. https://doi.org/10.2147/CIA.S153113.

[25] Ng, Q. X.; Ho, C. Y. X.; Koh, S. S. H.; Tan, W. C.; Chan, H. W. Doll Therapy for Dementia Sufferers: A Systematic Review. *Complementary Therapies in Clinical Practice* **2017**, *26*, 42–46. https://doi.org/10.1016/j.ctcp.2016.11.007.

[26] Pezzati, R.; Molteni, V.; Bani, M.; Settanta, C.; Di Maggio, M. G.; Villa, I.; Poletti, B.; Ardito, R. B. Can Doll Therapy Preserve or Promote Attachment in People with Cognitive, Behavioral, and Emotional Problems? A Pilot Study in Institutionalized Patients with Dementia. *Front. Psychol.* **2014**, *5*. https://doi.org/10.3389/fpsyg.2014.00342.

[27] Bisiani, L.; Angus, J. Doll Therapy: A Therapeutic Means to Meet Past Attachment

Needs and Diminish Behaviours of Concern in a Person Living with Dementia--a Case Study Approach. *Dementia (London)* **2013**, *12* (4), 447–462. https://doi.org/10.1177/1471301211431362.

[28] Browne, C. J.; Shlosberg, E. Attachment Theory, Ageing and Dementia: A Review of the Literature. *Aging Ment Health* **2006**, *10* (2), 134–142. https://doi.org/10.1080/13607860500312118.

[29] Miesen, B. M. L. Alzheimer's Disease, the Phenomenon of Parent Fixation and Bowlby's Attachment Theory. *International Journal of Geriatric Psychiatry* **1993**, *8* (2), 147–153. https://doi.org/10.1002/gps.930080207.

[30] Stephens, A.; Cheston, R.; Gleeson, K. An Exploration into the Relationships People with Dementia Have with Physical Objects: An Ethnographic Study: *Dementia* **2012**. https://doi.org/10.1177/1471301212442585.

[31] Mitchell, G.; McCormack, B.; McCance, T. Therapeutic Use of Dolls for People Living with

[32] Dementia: A Critical Review of the Literature: *Dementia* **2014**. https://doi.org/10.1177/1471301214548522.

[33] James, I. A.; Mackenzie, L.; Mukaetova-Ladinska, E. Doll Use in Care Homes for People w-
ith Dementia. *Int J Geriatr Psychiatry* **2006**, *21* (11), 1093–1098. https://doi.org/10.1002/gps.1612.

[34] Shin, J. H. Doll Therapy: An Intervention for Nursing Home Residents with Dementia. *J Psychosoc Nurs Ment Health Serv* **2015**, *53* (1), 13–18. https://doi.org/10.3928/02793695- 20141218-03.

[35] Green, L.; Matos, P.; Murillo, I.; Neushotz, L.; Popeo, D.; Aloysi, A.; Samuel, J.; Craig, E.; Porter, C.; Fitzpatrick, J. J. Use of Dolls as a Therapeutic Intervention: Relationship to Previous Negative Behaviors and pro Re Nata (Prn) Haldol Use among Geropsychiatric Inpatients. *Arch Psychiatr Nurs* **2011**, *25* (5), 388–389. https://doi.org/10.1016/j.apnu.2011.05.003.

[36] Braden, B. A.; Gaspar, P. M. Implementation of a Baby Doll Therapy Protocol for People with Dementia: Innovative Practice. *Dementia (London)* **2015**, *14* (5), 696–706. https://doi.org/10.1177/1471301214561532.

[37] Boutron, I.; Moher, D.; Altman, D. G.; Schulz, K. F.; Ravaud, P.; CONSORT Group. Extending the CONSORT Statement to Randomized Trials of Nonpharmacologic Treatment: Explanation and Elaboration. *Ann. Intern. Med.* **2008**, *148* (4), 295–309. https://doi.org/10.7326/0003-4819-148-4-200802190-00008.

[38] Kim, J.; Shin, W. How to Do Random Allocation (Randomization). *Clin Orthop Surg* **2014**, *6* (1), 103–109. https://doi.org/10.4055/cios.2014.6.1.103.

[39] Cohen-Mansfield, J.; Marx, M. S.; Dakheel-Ali, M.; Regier, N. G.; Thein, K. Can Persons with Dementia Be Engaged with Stimuli? *Am J Geriatr Psychiatry* **2010**, *18* (4), 351–362. https://doi.org/10.1097/jgp.0b013e3181c531fd.

[40] Wing, L.; Leekam, S. R.; Libby, S. J.; Gould, J.; Larcombe, M. The Diagnostic Interview for Social and Communication Disorders: Background, Inter-Rater Reliability and Clinical Use. *J Child Psychol Psychiatry* **2002**, *43* (3), 307–325. https://doi.org/10.1111/1469-7610.00023.

[41] Fenzio, F. *Manuale di consulenza pedagogica in ambito familiare, giuridico e scolastico*; Youcanprint, 2017. Olin, K. Perceived Caregiver Burden as a Function of Differential Coping Strategies: (410202005-016), 1995. https://doi.org/10.1037/e410202005-016.

[42] Marvardi, M.; Mattioli, P.; Spazzafumo, L.; Mastriforti, R.; Rinaldi, P.; Polidori, M. C.; Cherubini, A.; Quartesan, R.; Bartorelli, L.; Bonaiuto, S.; Cucinotta, D.; Di Iorio, A.; Gallucci,

M.; Giordano, M.; Martorelli, M.; Masaraki, G.; Nieddu, A.; Pettenati, C.; Putzu, P.; Solfrizzi, V.; Tammaro, A. E.; Tomassini, P. F.; Vergani, C.; Senin, U.; Mecocci, P.; Study Group on Brain Aging; Italian Society of Gerontology and Geriatrics. The Caregiver Burden Inventory in Evaluating the Burden of Caregivers of Elderly Demented Patients: Results from a Multicenter Study. *Aging Clin Exp Res* **2005**, *17* (1), 46–53. https://doi.org/10.1007/bf03337720.

[43] 51(43) Bellelli, G.; Morandi, A.; Davis, D. H. J.; Mazzola, P.; Turco, R.; Gentile, S.; Ryan, T.; Cash, H.; Guerini, F.; Torpilliesi, T.; Del Santo, F.; Trabucchi, M.; Annoni, G.; MacLullich, A. M. J. Validation of the 4AT, a New Instrument for Rapid Delirium Screening: A Study in 234 Hospitalised Older People. *Age Ageing* **2014**, *43* (4), 496–502. https://doi.org/10.1093/ageing/afu021.

[44] Pfeiffer, E. A Short Portable Mental Status Questionnaire for the Assessment of Organic Brain Deficit in Elderly Patients†. *Journal of the American Geriatrics Society* **1975**, *23* (10), 433–441. https://doi.org/10.1111/j.1532-5415.1975.tb00927.x.

[45] Katz, S.; Downs, T. D.; Cash, H. R.; Grotz, R. C. Progress in Development of the Index of ADL. *Gerontologist* **1970**, *10* (1), 20–30. https://doi.org/10.1093/geront/10.1_part_1.20.

[46] Faul, F.; Erdfelder, E.; Lang, A.-G.; Buchner, A. G*Power 3: A Flexible Statistical Power Analysis Program for the Social, Behavioral, and Biomedical Sciences. *Behavior Research Methods* **2007**, *39* (2), 175–191. https://doi.org/10.3758/BF03193146.

[47] Balzotti, A.; Filograsso, M.; Altamura, C.; Fairfield, B.; Bellomo, A.; Daddato, F.; Vacca, R. A.; Altamura, M. Comparison of the Efficacy of Gesture-Verbal Treatment and Doll Therapy for Managing Neuropsychiatric Symptoms in Older Patients with Dementia. *International Journal of Geriatric Psychiatry* **2019**, *34* (9), 1308–1315. https://doi.org/10.1002/gps.4961.

[48] Cantarella, A.; Borella, E.; Faggian, S.; Navuzzi, A.; De Beni, R. Using Dolls for Therapeutic 18 Purposes: A Study on Nursing Home Residents with Severe Dementia. *Int J Geriatr Psychiatry* **2018**, *33* (7), 915–925. https://doi.org/10.1002/gps.4872.

[49] Moyle, W.; Murfield, J.; Jones, C.; Beattie, E.; Draper, B.; Ownsworth, T. Can Lifelike Baby Dolls Reduce Symptoms of Anxiety, Agitation, or Aggression for People with Dementia in Long-Term Care? Findings from a Pilot Randomised Controlled Trial. *Aging Ment Health* **2019**, *23* (10), 1442–1450. https://doi.org/10.1080/13607863.2018.1498447.

[50] Yilmaz, C. K.; Aşiret, G. D. The Effect of Doll Therapy on Agitation and Cognitive State in Institutionalized Patients With Moderate-to-Severe Dementia: A Randomized Controlled Study. *J Geriatr Psychiatry Neurol* **2020**, 891988720933353. https://doi.org/10.1177/0891988720933353.

[51] Feng, Z.; Coots, L. A.; Kaganova, Y.; Wiener, J. M. Hospital and ED Use among Medicare Beneficiaries with Dementia Varies by Setting and Proximity to Death. *Health Aff (Millwood)* **2014**, *33* (4), 683–690. https://doi.org/10.1377/hlthaff.2013.1179.

[52] Phelan, E. A.; Borson, S.; Grothaus, L.; Balch, S.; Larson, E. B. Association of Incident Dementia with Hospitalizations. *JAMA* **2012**, *307* (2), 165–172. https://doi.org/10.1001/jama.2011.1964.

[53] White, N.; Leurent, B.; Lord, K.; Scott, S.; Jones, L.; Sampson, E. L. The Management of Behavioural and Psychological Symptoms of Dementia in the Acute General Medical Hospital: A Longitudinal Cohort Study. *Int J Geriatr Psychiatry* **2017**, *32* (3), 297–305. https://doi.org/10.1002/gps.4463.

[54] Hessler, J. B.; Schäufele, M.; Hendlmeier, I.; Junge, M. N.; Leonhardt, S.; Weber, J.; Bickel, H. Behavioural and Psychological Symptoms in General Hospital Patients with Dementia, Distress for Nursing Staff and Complications in Care: Results of the General Hospital Study. *Epidemiol Psychiatr Sci* **2018**, *27* (3), 278–287. https://doi.org/10.1017/S2045796016001098.

[55] Jurgens, F. J.; Clissett, P.; Gladman, J. R. F.; Harwood, R. H. Why Are Family Carers of People with Dementia Dissatisfied with General Hospital Care? A Qualitative Study. *BMC Geriatr* **2012**, *12*, 57. https://doi.org/10.1186/1471-2318-12-57.

[56] Kennedy, M.; Koehl, J.; Shenvi, C. L.; Greenberg, A.; Zurek, O.; LaMantia, M.; Lo, A. X. The Agitated Older Adult in the Emergency Department: A Narrative Review of Common Causes and Management Strategies. *J Am Coll Emerg Physicians Open* **2020**, *1* (5), 812–823. https://doi.org/10.1002/emp2.12110.

[57] Salari, S. M. Intergenerational Partnerships in Adult Day Centers: Importance of Age-Appropriate Environments and Behaviors. *Gerontologist* **2002**, *42* (3), 321–333. https://doi.org/10.1093/geront/42.3.321.