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Title: Apathy and its response to antipsychotic review and non-pharmacological interventions in people with dementia living in nursing homes: WHELD - A factorial cluster randomised controlled trial

Running title: Apathy and its response in WHELD cluster RCT

Authors and affiliations:

Anto P. Rajkumar, MD, PhD[1-3], Clive Ballard, MD[1,2], Jane Fossey, DPsych[4], Anne Corbett, PhD[1], Bob Woods[5], Martin Orrell[6], Rohan Prakash[7], Esme Moniz-Cook[8], Ingelin Testad[1]

[1] Department of Old Age Psychiatry, Institute of Psychiatry, Psychology, & Neuroscience, King's College London, London, UK

[2] Mental Health of Older Adults and Dementia Clinical Academic Group, South London and Maudsley NHS foundation Trust, London, UK

[3] Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark

[4] Oxford Health NHS Foundation Trust, UK

[5] North Wales Organisation for Randomised Trials in Health, Bangor University, UK

[6] Institute of mental health, University of Nottingham, UK

[7] University College London, London, UK

[8] Faculty of Health and Social Sciences, University of Hull, UK

Corresponding author:

Anto Praveen Rajkumar, MD, DNB, MRCPsych, PhD, PhD,

Clinical Lecturer,

Department of Old Age Psychiatry,

Institute of Psychiatry, Psychology, & Neuroscience,

King's College London,

16, De Crespigny Park,

London - SE5 8AF, United Kingdom,

Email: Anto.Rajamani@kcl.ac.uk

Phone : +44 02032289520

Fax : +44 02032289533

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Abstract

Objectives: Apathy is common, impactful, and difficult to manage in people with dementia. We evaluated the efficacy of non-pharmacological interventions, exercise and social interaction, in combination with antipsychotic review, to reduce apathy in people with dementia living in nursing homes in a cluster randomised controlled trial (RCT).

Methods: Well-being and health for people with dementia (WHELD) programme included a 2X2X2 factorial cluster RCT involving people with dementia living in 16 nursing homes in UK. All homes received training in person-centred care, and were randomised to receive antipsychotic review, social interaction, and exercise, either alone or in combinations. Apathy was one of the secondary outcomes of the WHELD trial, and it was measured by the Neuropsychiatric Inventory-nursing home version at baseline and nine months (N=273). We employed multilevel mixed effects linear regression models to assess the impact of the interventions on apathy.

Results: Prevalence of apathy was 44.0% (n=120; 95% CI 38.1-49.9%) at baseline. Severity of apathy had significant positive correlations with dementia severity, neuropsychiatric symptoms, depressive symptoms, agitation, and the needs of the people with dementia ($p<0.001$). Antipsychotic review reduced antipsychotic use, but it significantly increased apathy ($\beta=5.37$; SE=0.91; $p<0.001$). However, antipsychotic review in combination with either social interaction ($\beta=-5.84$; SE=1.15; $p<0.001$) or exercise ($\beta=-7.54$; SE=0.93; $p<0.001$) significantly reduced apathy.

Conclusions: Antipsychotic review can play a significant role in improving apathy in people with dementia living in nursing homes, when combined with psychosocial interventions such as social interaction and exercise. Guidance must be adapted to reflect this subtlety in care.

Introduction

Dementia affects 35 million people around the world. As the condition progresses many individuals move to reside in long-term care facilities. In the UK, these people account for one third of people with dementia [1], while 64% of people receiving Medicare in US nursing homes have dementia [2]. These individuals have complex needs due to the unique set of cognitive and functional impairments that characterise moderate to severe dementia. These are further compounded by neuropsychiatric symptoms, medical comorbidity and loss of communication ability [3]. Neuropsychiatric symptoms affect 90% of people with dementia at some point, and are particularly impactful with individuals requiring additional support to intiate and engage with activities [4]. Apathy is possibly the most frequent neuropsychiatric symptom, but is relatively underresearched.

Apathy is not merely a symptom, but a multidimensional syndrome affecting cognitive, emotional, and behavioural domains [5,6], and it causes clinically significant functional impairment in many people with dementia [7]. It is widely prevalent, persistent, and therapeutically challenging in people with dementia [8], especially those with moderate to severe dementia living in nursing homes [9]. A recent systematic review including 28 studies reported the mean prevalence of apathy in people with dementia living in nursing homes to be 36% (range: 17-82%) [9]. Moreover, apathy is associated with high levels of disability, faster cognitive and functional decline, weight loss, poor quality of life, high caregivers' burden, poor quality of care, poor rehabilitation, and increased risk of mortality [8,10-13].

Systematic research on the management of apathy remain sparse [10,14]. Acetylcholinesterase inhibitors have level II evidence to support their efficacy [14]. In the context of an increasing effort to reduce the use of antipsychotic medications in people with dementia, available evidence does not support the use of antipsychotics to treat apathy [14-16]. The literature regarding non-pharmacological treatments for apathy is limited [10], but some

preliminary studies indicate the potential of tailored therapeutic mentally stimulating activities [17], exercise [18], and social interaction [19].

As a part of a cluster randomised controlled trial focussing on people with dementia in nursing homes, we examined the impact of a pragmatic intervention to review antipsychotic medication. The initial results confirmed that this intervention could achieve a significant reduction in antipsychotic use, and that in combination with social interaction there was also a significant reduction in mortality. There was however a significant worsening in agitation and overall psychiatric symptoms, which was mitigated by social interaction and/or exercise [20]. This paper examines the frequency of apathy, determines whether review of antipsychotic medication led to any worsening of apathy and whether this could be mitigated by evidence based non-pharmacological interventions.

Material and Methods

Study design: Well-being and health for people with dementia (WHELD) programme included this cluster randomised controlled trial with 2X2X2 factorial design with two replications [21]. As the methodology employed in this study has been reported in detail elsewhere [20], it is only briefly presented here. The unit of randomisation was the nursing home. Each nursing home (cluster) received a randomly allocated intervention, with most homes randomly assigned to more than one of the three interventions, for nine months. The study received ethical approval from South-Central Oxford Research Ethics Committee C (REC number 11/SC0066). The trial is registered as a clinical trial (ISRCTN number 40313497), and the protocol is available online at http://www.kcl.ac.uk/ioppn/depts/wolfson/about/people/staff/ballardclive.aspx.

Setting: This study was conducted in 16 nursing homes in UK. Each care home represented a cluster that received a randomly allocated intervention for nine months. These nursing homes

were identified from those rated 'adequate' or better in the care quality commission register in 2013, in the Oxfordshire, Buckinghamshire, and London localities. Eight homes were selected by probability sampling, and the remaining eight were selected by non-probability sampling. We excluded the nursing homes, if less than 60% of their residents had dementia or they were in receipt of local authority special support.

Participants: All residents meeting eligibility criteria were invited to participate. Eligibility criteria included the diagnosis of dementia, defined by the Clinical Dementia Rating Scale (CDRS) [22] stage 1 or greater, and by Functional Assessment Staging (FAST) [23] stage 4 or greater. Consent for nursing home involvement was obtained from the management of the homes. If residents lacked capacity to consent, informed consent was obtained with the involvement of a nominated or personal consultee who represented the residents' interests and wishes in accordance with the Mental Capacity Act. Study interventions were delivered to all residents, with a minimum recruitment target of 12 participants per nursing home. The impact of study interventions on antipsychotic use, agitation, depression, neuropsychiatric symptoms, and mortality of these participants have already been reported elsewhere [20].

Interventions: WHELD therapists worked with care staff nominated as dementia champions in each home to implement the following four interventions, (i) *Person-Centred Care* (PCC): PCC was implemented using the tools from the Focussed Intervention for Training of Staff manual [24], based on evidenced based approaches for improving care in nursing homes, and from a review of other best available training manuals with the aim of personalising and tailoring care practice in line with individual preferences and needs [25]; (ii) *Antipsychotic review*: The WHELD therapists helped the homes' dementia champions to develop effective processes within the nursing homes to prompt antipsychotic review according to the best practice guidelines. Moreover, they worked with the physicians and nursing home staff to augment PCC during the antipsychotic withdrawal period. The participants' primary care

physicans or specialist psychiatrists reviewed long-term prescriptions of antipsychotics on the basis of the National Institute for Health and Care Excellence (NICE) dementia guidelines [26] and of the antipsychotic care pathway, developed by the Alzheimer's Society in partnership with the Department of Health [27]. These guidelines emphasised careful medical assessment of underlying causes of neuropsychiatric symptoms such as pain and factors leading to delirium, the use of nonpharmacological interventions as a first-line approach before considering pharmacotherapy (unless symptoms were severe or involving immediate risks), regular review of antipsychotic prescriptions in people on long-term antipsychotic medications, and the recommendation to constrain treatment periods with newly commenced antipsychotics to a maximum duration of 12 weeks. A trial discontinuation was recommended as the preferred practice for patients who had had antipsychotic prescriptions for more than 3 months, but caution was recommended in people with baseline Neuropsychiatric Inventory scores above 14 on the basis of evidence from a previous randomised controlled trial [28]; (iii) *Exercise*: enjoyable positive physical activities were encouraged on the basis of the Seattle protocols [29], and exercise elements of the NEST manual [30]. Previous and current interests of the participants, and their current level of health and fitness were assessed. The aim was for participants to be engaged in at least one hour of exercise per week. If they were doing this at baseline, the amount of exercise was increased by 20% by the end of the intervention period; (iv) *Social interaction with pleasant activities*: A social interaction intervention manual was developed on the basis of three evidence based approaches, the positive events schedule from the Seattle protocols [29], the social activities elements of the NEST manual [30], and the social interaction intervention, developed by Cohen-Mansfield and colleagues [31]. Individualised plans for activities and staff-resident interactions were developed using a life history appproach and assessment of current interests. The aim was for participants to be engaged in

at least one hour of social interaction per week. If this was taking place at baseline, the amount of social interaction was increased by 20% by the end of the intervention period.

Randomisation*:* All 16 nursing homes received PCC. After constrained complete list randomisation, stratified on the three participating sites [32], antipsychotic review, exercise, and social interaction were implemented in eight care homes each. The constraint ensured an approximately equal distribution of the number of study interventions to each geographic location. Eight nursing homes were randomly assigned to antipsychotic review, eight to an intervention to increase social interaction, and eight to an exercise intervention. Each possible combination of interventions was assigned to two nursing homes exclusively. A trained WHELD therapist coordinated each intervention into the eight nursing homes that were randomised to receive that intervention. In each nursing home, a minimum of two lead care staff members were trained to implement that intervention.

Outcome measures: Apathy was one of the outcomes of the WHELD trial, and it was was assessed by the Neuropsychiatric Inventory Nursing Home version (NPI-NH) [33]. G domain of NPI-NH evaluated apathy over the four weeks prior to assessment using a screening question, and seven sub-questions. When apathy was identified, NPI-NH documented its frequency in four-point scale, and its severity in a three-point scale. An apathy domain score was calculated by multiplying frequency and severity scores. This score was zero, when apathy was absent, and it ranged from one to 12, when apathy was present. Depression, anxiety, and agitation of the participants were evaluated using the Cornell Scale for Depression in Dementia (CSDD) [34], Rating Anxiety In Dementia (RAID) [35], and Cohen-Mansfield Agitation Inventory (CMAI) [36], respectively. Needs and quality of life of the participants were systematically assessed using the Camberwell Assessment of Need for the Elderly (CANE) [37], and assessment of quality of life for people with dementia (DEMQoL) [38], respectively. Assessments were carried out at baseline before randomisation, and after the

completion of nine month-long interventions by research assistants, blind to intervention allocation. The factorial design with all nursing homes receiving at least one intervention helped in maintaining the blinding.

Statistical analyses: We analysed the data from WHELD cluster randomised controlled trial using data pertaining to apathy from the same randomised participants reported previously [20,21]. Participants' characteristics, their clinical profile, and apathy scores were initially analysed by descriptive statistics. Missing values of items within the study questionnaires were replaced with the mean scores of the remaining items in the questionnaires as long as the number of missing items did not exceed 20% of the total number of items in the questionnaires. Prevalence of apathy at baseline was compared with that after the nine months intervention period using the McNemar's test. Statistical significance of difference between the NPI-NH G domain apathy scores at the two time points was analysed by the Wilcoxon signed-rank test. Appropriate statistical tests of significance were employed to analyse the observed differences between the participants with and without apathy. Correlations between apathy scores and CDR, FAST, CSDD, RAID, CMAI, CANE, as well as DEMQoL scores were assessed using Spearman's rank-order correlation with Bonferroni corrections at baseline and after the nine months intervention period.

The impact of antipsychotic review on apathy in people with dementia living in nursing homes was analysed by multilevel mixed effects linear regression models with maximum likelihood estimation method. Further analyses were undertaken to determine the impact of combining antipsychotic review with social interaction or exercise. Individual participants were nested within a higher level, the nursing homes. Differences between the NPI-NH apathy scores at the two time points was the outcome variable. Study interventions were the independent variables. Age and gender of the participants, as well as FAST and CSDD scores at baseline were included as covariates. Although FAST stages were naturally

ordered, they were modelled as linear effects to increase the power of the statistical analyses. Participants that did not receive any interventions except the PCC intervention formed the reference group. Clustered robust standard errors for the estimated regression coefficients were calculated with the nursing homes as the clustering variable. Only the participants that completed the nine months intervention period were included in these analyses. We repeated these analyses by including only the participants with moderately severe and severe dementia, defined by FAST stages six and seven at baseline. All analyses were performed using the statistical software STATA 13.1 (StataCorp, Texas, USA).

Results

Participant characteristics: 273 people with dementia living in 16 nursing homes were assessed for apathy at baseline, and 191 (70.0%) of them completed the nine months intervention period. Figure 1 presents the participant flow diagram of the WHELD RCT. Presence of apathy at baseline was not significantly associated with death (χ^2=0.10; df=1; p=0.75), but was significantly associated with withdrawal from the study (χ^2=8.04; df=1; p=0.005). Table 1 presents the baseline characteristics of participants with and without apathy. 73.6% (95% CI 68.0-78.5%) of the participants were women, and 89.0% (95% CI 84.7-92.2%) of them were Caucasian. Mean age of the participants was 85.3 (95% CI 84.4-86.1) years at baseline. Age of the participants did not differ significantly between the 16 nursing homes (Kruskal-Wallis χ^2=16.18; df=15; p=0.37). Table 2 presents baseline characteristics of the participants, who received and did not receive antipsychotic review, social interaction, and exercise.

Prevalence and correlates of apathy: 120 participants (44.0%; 95% CI 38.1-49.9%) had apathy at baseline. Mean NPI-NH G domain apathy scores at baseline was 2.32 (95% CI 1.91-2.73). Participants with and without apathy at baseline did not differ significantly in

gender, age, ethnicity, number of years lived in the nursing homes, or the current prescription of antipsychotic medications. Table 3 presents the correlations between NPI-NH apathy scores, and severity of dementia, neuropsychiatric symptoms, depressive symptoms, anxiety symptoms, agitation, quality of life, and the needs of the people with dementia at baseline and after the nine months intervention period. Severity of apathy at baseline showed significant positive correlations with severity of dementia, overall neuropsychiatric symptoms, depression, agitation, and overall needs after Bonferroni corrections ($p<0.001$). 85 participants (44.5%; 95% CI 37.5-51.7%) had apathy after the nine months intervention period. Mean NPI-NH apathy scores at follow-up was 2.60 (95% CI 2.08-3.13). Categorical presence of apathy among the participants did not change significantly between the two time points (McNemar's $\chi^2=0.47$; df=1; p=0.49), and the numerical increase in the NPI-NH apathy scores at follow-up was not statistically significant (Wilcoxon matched-pairs signed-rank test z=1.48; p=0.14). However, increased apathy correlated with increased severity of dementia ($r_s=0.15$; p=0.04), and with increased needs of the people with dementia ($r_s=0.20$; p=0.007) between the two time points. Moreover, it showed significant negative correlation with the changes in the quality of life for the people with dementia during the study ($r_s=-0.15$; p=0.04).

Impact of antipsychotic review on apathy: Antipsychotic review alone significantly increased apathy (β=5.37; SE=0.91; $p<0.001$), (Cohen's d=-0.97). However, antipsychotic review in combination with either social interaction (Cohen's d=0.49) or exercise (Cohen's d=0.20) reduced apathy, and this reduction was statistically significant, after adjusting for the effects of age, gender, baseline dementia severity, and baseline depressive symptoms (Table 4). Further analyses including only the participants with moderately severe and severe dementia confirmed that antipsychotic review (β=6.75; SE=1.31; $p<0.001$), when delivered alone, significantly increased the severity of apathy, and that antipsychotic review in

combination with either social interaction (β=-6.59; SE=1.58; p<0.001) or exercise (β= -10.51; SE=1.32; p<0.001) significantly reduced the severity of apathy, after adjusting for the effects of age, gender, baseline dementia severity, and baseline depressive symptoms. Moreover, analyses including only the participants, who did not receive any antipsychotics at the baseline, confirmed that antipsychotic review (β=4.24; SE=1.55; p=0.006), when delivered alone, significantly increased the severity of apathy, and that antipsychotic review in combination with either social interaction (β=-4.10; SE=1.86; p=0.03) or exercise (β= -8.93; SE=1.97; p<0.001) significantly reduced the severity of apathy, after adjusting for the effects of age, gender, baseline dementia severity, and baseline depressive symptoms.

Apathy and depression: Mean CSDD score of the people with dementia was 5.00 (95% CI 4.46-5.54) at baseline, and 4.59 (95% CI 3.93-5.25) after the nine month intervention period (Wilcoxon matched-pairs signed-rank test z=0.07; p=0.94). Correlation between the changes in the severity of apathy and the changes in the severity of depressive symptoms during the study was not statistically significant (r_s=0.08; p=0.30). Changes in the severity of apathy between the two time points did not significantly change the severity of depressive symptoms (β=0.10; SE=0.08; p=0.22), after adjusting for the effects of age, gender, and baseline dementia severity of the participants.

Discussion

This study has confirmed that apathy is common in people with dementia living in nursing homes, and identified significant correlations with the severity of dementia and other neuropsychiatric symptoms. Worsening of apathy over nine months of follow-up was significantly associated with increased overall needs, and with worsening quality of life. Importantly, antipsychotic review was associated with worsening apathy. However, when antipsychotic review was undertaken in combination with social interaction or personalised

exercise, this not only mitigated the apparent detrimental impact but led to significant improvement. Changes in the severity of apathy were not significantly correlated with the changes in the severity of depressive symptoms, providing further evidence that apathy is an independent neuropsychiatric syndrome. Correlations of apathy with CMAI, CSDD, and RAID scores were not statistically significant after follow-up. This finding may be explained either by smaller numbers at the follow-up or by distinct progressive courses of these neuropsychiatric symptoms associated with dementia.

The detrimental impact of antipsychotic review on apathy is an important point, and consistent with detrimental effects on other neuropsychiatric symptoms (26). Antipsychotic review was conducted by following guidance on managing neuropsychiatric symptoms that was published during the UK government drive to reduce antipsychotic use in the last five years, which has led to substantial reductions. This guidance has led to a shift in the landscape of antipsychotic prescribing in the UK whereby people now receiving antipsychotic medications have more severe neuropsychiatric symptoms than the previous cohorts. The additional evidence from this study that discontinuation of antipsychotics also impacts upon apathy adds weight to the need for review of the existing guidelines including greater emphasis on the use of evidence-based non-pharmacological interventions in conjunction with antipsychotic review.

Prevalence of apathy among the participants of this study was similar to the mean prevalence of apathy, reported by a recent systematic review [9], in people with dementia living in nursing homes. Our findings corroborate previous studies that have reported the importance of apathy in increasing needs and worsening quality of life of people with dementia [12,19,39]. Categorical presence of apathy among the participants did not change significantly between the two time points of this study. Moreover, apathy and depressive symptoms differed on their courses and their responses to study interventions [20]. Such

persistence, prognostic significance, and distinctness from depression argue for the nosological validity of apathy as a separate neuropsychiatric syndrome. Recognising apathy as a separate syndrome and validating proposed diagnostic criteria for apathy [40] will reduce under-recognition [41] and should lead to improvement of its management in people with dementia.

Strengths of this study include a robust design, with a relatively large sample size and long follow-up period, the inclusion of people with moderately severe and severe dementia and high retention of surviving participants. The interventions followed best practice guidelines for antipsychotic review and evidence based approaches for SI and analyses explored the effects of combined interventions. Selection bias was minimised by randomisation, and by including all eligible consenting residents in the nursing homes. Observer bias was reduced by blinding the research assistants, who assessed outcomes, to intervention allocation. Contamination was avoided by the cluster RCT design. It is important to acknowledge some limitations of the study. Definition of apathy is still evolving [42], and standardised assessment guidelines to diagnose apathy are lacking [6,10]. Reduction of apathy was not the primary outcome of the WHELD trial, and the randomisation did not stratify the participants on the presence of apathy [20]. Moreover, our analyses considered all subtypes of dementia as one category, but the effects of studied interventions on apathy in people with various subtypes of dementia may differ. Furthermore, the pragmatic nature of this RCT allowed including people with multiple concurrent medications.

Weak evidence base for available non-pharmacological interventions for apathy in people with dementia may be attributed to poor quality of research rather than lack of efficacy of these interventions [10]. Apathy in people with dementia, including those with severe dementia living in nursing homes, can be approached with therapeutic optimism. Significant reduction in the severity of apathy can be achieved, if judicial review of

pharmacological interventions is combined with appropriate non-pharmacological interventions. Standardising assessment guidelines and diagnostic criteria for apathy is essential to evaluate the efficacy of potential interventions, and to investigate the neurobiological mechanisms underlying apathy. More large and rigorous RCTs investigating the efficacy of combined pharmacological and non-pharmacological interventions to reduce apathy in people with dementia are needed.

Conclusion

This study confirms the high prevalence and impact of apathy in people with dementia living in nursing homes. Of particular note, review of antipsychotic medication as a single therapeutic intervention led to a significant worsening in apathy. However, undertaking antipsychotic review in conjunction with the implementation of evidence based non-pharmacological interventions led to significant improvements. The results emphasise the importance of amending current best practice guidelines to emphasise the importance of implementing non-pharmacological interventions as part of the process of reviewing and discontinuing antipsychotic medication in people with dementia.

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Table 1: Baseline characteristics of participants with (n=120) and without apathy (n=153)

Characteristic		Without apathy n (%) / Mean (SD)	With apathy [a] n (%) / Mean (SD)	χ^2 / t [b] / z [c]	p
Female gender		113 (73.9)	88 (73.3)	0.01	0.92
Age in years		85.7 (6.8)	84.7 (7.0)	1.13 [c]	0.26
Ethnicity: Caucasian		136 (88.9)	107 (89.2)	0.01	0.94
Years lived in nursing homes		2.1 (2.0)	2.5 (2.2)	-1.21 [c]	0.22
CDR	Mild (0.5-1)	28 (18.3)	5 (4.2)	25.34	< 0.001
	Moderate (2)	72 (47.1)	40 (33.3)		
	Severe (3)	53 (34.6)	75 (62.5)		
FAST	Mild	25 (16.3)	5 (4.2)	15.35	0.002
	Moderate	12 (7.8)	4 (3.3)		
	Moderately severe	94 (61.4)	82 (68.3)		
	Severe	22 (14.4)	29 (24.2)		
NPI-NH total score [d]		9.7 (11.4)	25.5 (18.5)	-8.72 [c]	< 0.001
CMAI total score		43.7 (15.0)	53.8 (17.5)	-5.07 [c]	< 0.001
CSDD total score		4.2 (4.2)	6.1 (4.6)	-4.03 [c]	< 0.001
RAID total score		4.5 (4.4)	6.0 (5.6)	-2.24 [c]	0.03
CANE total number of needs		14.4 (2.4)	16.1 (2.8)	-5.38 [b]	< 0.001
DEMQoL total score		105.4 (12.2)	102.6 (12.6)	2.13 [c]	0.03
Currently on antipsychotics		22 (14.4)	26 (21.7)	2.46	0.12

[a] Neuropsychiatric inventory- nursing home version (NPI-NH) G domain, apathy, score above 0; [b] Two-sample t test with equal variances; [c] Two-sample Wilcoxon rank-sum test z value; CDR: Clinical Dementia Rating; FAST: Functional Assessment Staging Test; [d] Total score of all 12 domains of NPI-NH; CMAI: Cohen-Mansfield agitation inventory; CSDD: Cornell Scale for Depression in Dementia; RAID: Rating anxiety in dementia; CANE: Camberwell assessment of need for the elderly; DEMQoL: Assessment (Proxy) of quality of life for people with dementia

Table 2: Baseline characteristics of participants, who received and did not receive antipsychotic review, social interventions, and exercise

Characteristic		AR (n=143) n (%) / Mean (SD)	No AR (n=130) n (%) / Mean (SD)	SI (n=138) n (%) / Mean (SD)	No SI (n=135) n (%) / Mean (SD)	EX (n=136) n (%) / Mean (SD)	No EX (n=137) n (%) / Mean (SD)
Female gender		107 (74.8)	94 (72.3)	94 (68.1)	107 (79.3)	92 (67.7)	109 (80.0)
Age in years		85.4 (6.9)	85.1 (7.0)	84.7 (7.3)	85.8 (6.4)	85.3 (6.5)	85.2 (7.3)
Ethnicity: Caucasian		129 (90.2)	114 (87.7)	118 (85.5)	125 (92.6)	118 (86.8)	125 (91.2)
Years lived in nursing homes		2.5 (2.1)	2.1 (2.1)	2.4 (2.4)	2.2 (1.8)	2.5 (2.3)	2.0 (1.9)
CDR	Mild (0.5-1)	19 (13.3)	14 (10.8)	13 (9.4)	20 (14.8)	17 (12.5)	16 (11.7)
	Moderate (2)	59 (41.3)	53 (40.8)	49 (35.5)	63 (46.7)	51 (37.5)	61 (44.5)
	Severe (3)	65 (45.5)	63 (48.5)	76 (55.1)	52 (38.5)	68 (50.0)	60 (43.8)
FAST	Mild	19 (13.3)	11 (8.5)	7 (5.1)	23 (17.0)	13 (9.6)	17 (12.4)
	Moderate	8 (5.6)	8 (6.2)	7 (5.1)	9 (6.7)	6 (4.4)	10 (7.3)
	Moderately severe	92 (64.3)	84 (64.6)	91 (65.9)	85 (63.0)	89 (65.4)	87 (63.5)
	Severe	24 (16.8)	27 (20.8)	33 (23.9)	18 (13.3)	28 (20.6)	23 (16.8)
NPI-NH total score [d]		15.3 (16.3)	18.1 (17.4)	17.6 (17.2)	15.6 (16.4)	14.7 (16.5)	18.5 (17.0)

NPI-NH apathy score [a]	2.0 (3.2)	2.7 (3.7)	2.2 (3.4)	2.4 (3.5)	2.1 (3.3)	2.6 (3.5)
CMAI total score	47.2 (15.8)	48.9 (18.0)	49.1 (16.6)	46.9 (17.1)	47.1 (15.9)	49.0 (17.8)
CSDD total score	4.4 (4.0)	5.6 (4.8)	5.3 (4.2)	4.7 (4.7)	4.7 (4.2)	5.3 (4.7)
RAID total score	4.8 (4.4)	5.6 (5.6)	5.3 (4.8)	5.1 (5.2)	5.2 (5.0)	5.2 (5.1)
CANE total number of needs	15.0 (2.6)	15.3 (2.8)	15.6 (2.9)	14.7 (2.5)	15.3 (2.5)	15.0 (2.9)
DEMQoL total score	105.9 (9.4)	102.2 (15.0)	106.0 (11.8)	102.4 (12.9)	105.0 (12.1)	103.3 (12.8)
Currently on antipsychotics	25 (17.5)	23 (17.7)	13 (9.4)	35 (25.9)	29 (21.3)	19 (13.9)

[a] Neuropsychiatric inventory- nursing home version (NPI-NH) G domain apathy scores; CDR: Clinical Dementia Rating; FAST: Functional Assessment Staging Test; [d] Total score of all 12 domains of NPI-NH; CMAI: Cohen-Mansfield agitation inventory; CSDD: Cornell Scale for Depression in Dementia; RAID: Rating anxiety in dementia; CANE: Camberwell assessment of need for the elderly; DEMQoL: Assessment (Proxy) of quality of life for people with dementia

Table 3: Clinical correlates of apathy [a] among people with dementia living in nursing homes

Clinical variable	At baseline [b] (n=273)	p [c]	At follow-up [d] (n=191)	p [c]
CDR score	0.34	< 0.001	0.37	< 0.001
FAST score	0.26	< 0.001	0.29	0.002
NPI-NH total score [e]	0.58	< 0.001	0.46	< 0.001
CMAI total score	0.31	< 0.001	0.16	1.00
CSDD total score	0.26	< 0.001	0.13	1.00
RAID total score	0.13	1.00	0.03	1.00
CANE total score	0.33	< 0.001	0.16	1.00
DEMQoL total score	-0.15	0.70	-0.08	1.00

[a] Neuropsychiatric inventory- nursing home version (NPI-NH) G domain, apathy, scores ranging from 0 to 12; [b] Spearman correlation coefficients at baseline; [c] p values after Bonferroni correction for multiple testing; [d] Spearman correlation coefficients after 9 months follow-up; CDR: Clinical Dementia Rating; FAST: Functional Assessment Staging Test; [d] Total score of all 12 domains of NPI-NH; CMAI: Cohen-Mansfield agitation inventory; CSDD: Cornell Scale for Depression in Dementia; RAID: Rating anxiety in dementia; CANE: Camberwell Assessment of Need for the Elderly; DEMQoL: Assessment (Proxy) of quality of life for people with dementia

Table 4: Changes in the severity of apathy [a] following antipsychotic review and non-pharmacological interventions in people with dementia living in nursing homes

Intervention	AR alone (n=43)	AR and SI (n=31)	AR and EX (n=27)
Baseline apathy score (Mean (SD))	1.37 (2.02)	1.77 (3.27)	2.74 (3.89)
Antipsychotic use at baseline (n (%))	6 (13.95)	1 (3.23)	9 (33.33)
Follow-up apathy score (Mean (SD))	4.13 (4.13)	2.28 (3.58)	1.05 (2.16)
Changes in apathy from baseline to follow-up (Mean (SD))	2.75 (4.09)	0.36 (4.10)	-1.05 (4.13)
Discontinuing antipsychotics (n (%)) [b]	5 (11.63)	0 (0.00)	2 (7.41)
Unadjusted difference in apathy between the groups (Mean (SD)) [c]	5.58 (4.31)	3.19 (4.35)	1.78 (4.39)
Adjusted difference in apathy between the groups (β) [d]	5.37	-5.84	-7.54
95% CI of β [e]	3.58 – 7.15	-8.10 – -3.58	-9.35 – -5.72
z	5.90	-5.06	-8.14
p value	< 0.001	< 0.001	< 0.001

[a] Neuropsychiatric inventory- nursing home version (NPI-NH) G domain, apathy, scores; [b] Number of people, who were on antipsychotics at baseline but not on antipsychotics at the follow-up; [c] Unadjusted differences among the changes in the severity of apathy from baseline to follow-up between the intervention arm and the participants that did not receive any interventions except the person-centred care (PCC) (n=33); [d] Regression coefficients, estimated by multilevel mixed effects linear regression model with the changes in the severity of apathy as the dependent variable, nursing homes as the clustering variable,

various interventions as the independent variables, and age and gender of the participants, as well as Functional Assessment Staging Test and Cornell Scale for Depression in Dementia scores at baseline as covariates. Participants that did not receive any interventions except PCC formed the reference group (n=33); [e] Clustered robust standard errors were calculated with

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Figure 1: CONSORT diagram showing flow of participants