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Impact of antipsychotic review and non-pharmacological intervention on antipsychotic use, neuropsychiatric symptoms and mortality in people with dementia living in nursing homes: WHELD - A factorial cluster randomised controlled trial

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Abstract

Objectives: To evaluate the impact of antipsychotic review, social interaction and Exercise in conjunction with person-centred care on antipsychotic use, agitation and depression in people with dementia living in nursing homes.

Methods: A cluster randomised factorial controlled trial with two replications conducted in people with dementia in 16 UK nursing homes. All homes received training in Person-centred care. Eight homes were randomised to AR, Social Interaction and Exerciserespectively. Outcome measures were antipsychotic use, agitation and depression. Secondary outcome measures were overall neuropsychiatric symptoms and mortality.

Results: Antipsychotic review significantly reduced antipsychotic use by 50% (OR 0.17, 95% CI 0.05 to 0.60, p=0.006). Antipsychotic review and Social Interaction significantly reduced mortality (OR=0.36, 95% CI 0.23 to 0.57, p<0.001) but showed significantly worse outcome in neuropsychiatric symptoms compared to the group receiving neither Antipsychotic Review nor Social Interaction (7.37 95% CI 1.53 to 13.22, p=0.017). This detrimental impact was mitigated by concurrent delivery of Social Interaction (-0.44, CI -4.39 to 3.52, p=0.82) but with no significant impact specifically on agitation. Exercise significantly improved depression (-3.41, CI 0.56 to 6.72, p=0.022) and neuropsychiatric symptoms (-4.01, 95% CI -7.91 to -0.10, p=0.045).

Conclusions: While reductions in antipsychotic use can be achieved using a 'real world' intervention, this may not be of benefit to people with dementia in the current climate of more judicious prescribing unless non-pharmacological interventions such as Social Interaction or Exercise are provided in parallel.

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Introduction

There are 35 million people with dementia worldwide, many of whom reside in nursing homes. In the UK one third of people with dementia live in care homes (1) and in the US 64% of people receiving Medicare in nursing homes have dementia (2). The majority of these individuals have moderate or severe dementia and have highly complex care needs resulting from a combination of cognitive, functional and communication impairments, neuropsychiatric symptoms and medical comorbidity. Neuropsychiatric symptoms such as aggression, agitation and psychosis affect 90% of people at some point during the course of their condition (3). They cause significant distress, and can place the individual and others at risk. Furthermore, they present a substantial challenge for health and care professionals as there are limited treatment options. As a result, many people are prescribed antipsychotic medications.

There is evidence to support modest benefits of antipsychotic treatment for some neuropsychiatric symptoms, particularly risperidone, olanzapine and aripiprazole for the short-term management of severe aggression but benefits with longer term treatment are less clear (4-7). Moreover, antipsychotics are associated with severe safety concerns including increased cognitive decline, stroke and death, particularly when used in the long term (5, 7-9). Best practice guidance emphasises the importance of frequent monitoring and judicious prescribing in order to reduce these risks, but also to ensure identification of cases where antipsychotic use is warranted (10, 11).

There is a growing evidence-base to support the value of person-centred care and non-pharmacological interventions for the management of neuropsychiatric symptoms in nursing homes (12-17). A recent meta-analysis particularly highlighted the benefit conferred by social interaction and pleasant activities on both neuropsychiatric symptoms and antipsychotic use (18), and of physical activity through personalized exercise on mood (19). This suggests that augmentation of person-centred care these elements would provide an effective approach to care.

Up to 2008, cohort studies and audits in the US and Europe reported that 40% of people with dementia in nursing homes were receiving an antipsychotic (20-22). In recent years there has been a concerted effort to reduce unnecessary prescribing of antipsychotics in people with dementia which has led to a shift in the landscape of their use, with audits demonstrating a 15-50% reduction in prescriptions across US and Europe (23-25). With this reduction in

unnecessary prescriptions, use of antipsychotics has likely been focussed to a greater extent on people with more severe neuropsychiatric symptoms, and may have altered the benefit to harm ratio. Whilst recent randomised discontinuation studies have reported benefits following review and withdrawal of antipsychotics (6), there are no randomised trials evaluating the impact of rigrous antipsychotic review.

This raises key questions regarding the potential to build an effective, feasible 'real world' intervention to manage neuropsychiatric symptoms and antipsychotic use in the complex landscape of nursing homes. It will be important to establish whether routine implementation of antipsychotic review and evidence-based non-pharmacological interventions would contribute to improved outcomes for people with dementia. This cluster randomised controlled trial evaluates an intervention to rigorously implement best practice guidelines for the prescribing and review of antipsychotics in people with dementia living in care homes alongside non-pharmacological approaches, delivered through primary care physician and nursing home education. The primary hypotheses were that antipsychotic review would reduce antipsychotic use, that social interaction would reduce agitation and that exercise would improve depression.

Method

Study design

A cluster randomised, 2X2X2 factorial design with two replications in 16 nursing homes in South London, North London, Oxfordshire and Buckinghamshire. The unit of randomization was the care home. Each care home (cluster) received a randomly allocated intervention, with most homes randomized to more than one of the three interventions for nine months (Figure 1). The study received ethical approval from South-Central Oxford REC C (11/SC0066). The trial is as a clinical trial (ISRCTN Ref: 40313497) and the protocol is available online at http://www.kcl.ac.uk/ioppn/depts/wolfson/about/people/staff/ballardclive.aspx.

Participants

Participants were people with dementia (defined using the Clinical Dementia Rating Scale (26) and Functional Assessment Staging (FAST) (27), with Stage 1 or greater or a score of 4 or greater, required for study inclusion respectively). Nursing homes were identified from those rated 'adequate' or better in the Care Quality Commission register in 2013. Eight homes were selected from a convenience sample and another eight randomly selected. Homes were

excluded if less than 60% of the residents had dementia or they were in receipt of local authority special support. All residents meeting eligibility criteria within the homes were invited to participate. Baseline and follow-up data were collected on all residents who consented and met the inclusion criteria at each participating nursing home.

Consent for nursing home involvement was obtained from the management of the homes. If residents lacked capacity, informed consent was obtained through the involvement of a nominated or personal consultee who represented the residents' interests and wishes in accordance with the Mental Capacity Act. Research assistants carried out baseline assessments prior to randomisation.

Interventions

All 16 homes received a Person-Centred Care intervention. Eight care homes were randomised to receive Antipsychotic Review, eight to Social Interaction and eight to Exercise (Figure 1). The interventions were delivered by a therapist, who had attended an intensive 10-day training programme and who coordinated the delivery of the intervention into all homes randomised to that intervention. In each home a minimum of two lead staff members (Champions) were trained to implement the intervention.

Person-Centred Care

The Person-Centred Care intervention primarily used tools developed in the published Focussed Intervention for Training of Staff (FITS) manual, which has demonstrated efficacy in a robust randomised controlled trial (13). Supplementary materials were drawn from the best available training manuals (14) and augmented by leadership training based on the principles identified in a systematic qualitative review of the elements of effective implementation (28) and input from an expert therapy development group . The intervention had five focal points:(i) Embedding an understanding of dementia and Person-Centred Care; (ii) Assessing how each home personalises care in terms of plans and provision of opportunities for individuals Person-Centred Care ; (iii) Developing staffs understanding of the relationship between an individual resident's experience, behavior and wellbeing through the use of life story and principles of functional analysis to understand challenging behaviour ; (iv) Recognising the impact of staff–resident interactions on the care experience using cognitive behavioural principles; (v) Implementing Person-Centred Care planning based on these principles. This training package was delivered to all staff in the participating homes

Antipsychotic Review

Antipsychotic Review focussed specifically on the review of antipsychotic prescriptions by primary care physicans or psychiatry specialists, based on the NICE dementia guidelines (28) and facilitated by antipsychotics guidance developed by Alzheimer's Society in partnership with the Department of HeaLth in the UK (10). The core of the guidelines and the related educational materials was consistent with best practice advice internationally, with educational materials describing the modest benfits and potential harmful effects of anti-psychotic medications in people with dementia. The guidelines emphasized careful medical assessment of underlying causes of neuropsychiatric symptoms such as pain and factors leading to delirium, the use of monitoring and/or non-pharmacological interventions as a first-line approach before considering pharmacotherapy (unless symptoms were severe or causing risk to the person or others), regular review of antipsychotic prescriptions in people already prescribed these treaments and advice to contain treatment periods with newly commenced antipsychotics to a maximum duration of 12 weeks when possible. A trial discontinuation was recommended as preferred practice for patients who had been prescribed antipsychotics for more than three months, but based on previous randomised controlled trial evidence caution was recommended in people with baseline NPI scores of >14 (29). Physicians were invited to an interactive seminar and/or practice meeting, provided with a toolkit or best practice guide (10) and given an opportunity for detailed discussion including scenarios with individual patients. Seminars were conducted for care staff regarding safe antipsychotic prescribing, monitoring and review. WHELD therapists worked with champions and other staff to develop processes to prompt physician review according to best practice guidelines. Therapists also worked with physicians and staff to augment Person-Centred Care during antipsychotic withdrawal. The goal was to promote informed review. Prescribing decisions were still entirely made by the participants' own physician. Iin the majority of cases this was their primary care physician.

Social Interaction with Pleasant Activities

An Social Interaction intervention manual was developed to operationalise the way social activities are selected with the aim of enhancing resident interactions with staff, family and volunteers and increasing the amount of time residents spend in meaningful activity. The objectives were to provide positive planned social interaction for each resident delivered through individual or group sessions through at least three sessions per week. The activities were based on three evidence-based approaches to promote Social Interaction and specific communication skills training to enhance staff–resident interactions. These were the published Positive Events Schedule (30), Social Interaction intervention (31) and N.E.S.T programme (32). Individualised care plans were developed taking into account life history information and

interests to ensure activities and interactions were individually tailored. The aim was for residents to have at least one hour a week of Social Interaction or to increase Social Interaction by 20% by the end of the study.

Exercise

The Exercise intervention aimed to promote exercise through enjoyable physical activities based on the Seattle protocols (30) and N.E.S.T manual (32). Assessment of interests informed a personalised exercise plan developed by the therapist and chamption, accounting for health and fitness levels. Walking was encouraged as a routine activity, where appropriate, alongside other individual and group activities such as dancing, exercise to music or chair volleyball. The aim was for residents to engage in at least one hour a week of exercise or to increase exercise by 20% by the end of the study.

Outcome measures

Antipsychotic and other psychotropic drugs were classified according to the British National Formulary. Depression was evaluated using the Cornell Scale for Depression in Dementia, an informant- and patient-reported scale validated for dementia (33). Agitation was evaluated by informant interview using the 29 item Cohen-Mansfield Agitation Inventory (CMAI) (34). Secondary outcomes included neuropsychiatric symptoms measured through the ten domains of the Neuropsychiatric Inventory Nursing Home version (35) (NPI-NH) (which also includes a domain for depression), mortality and dementia severity (CDR and FAST) (26, 27).

Assessments were carried out at baseline and nine months by research assistants blind to intervention allocation. The factorial design made it more straightforward than usual in trials of a non-pharmacological intervention to maintain blinding.

Randomisation

Randomisation was performed as a constrained complete list randomisation stratified on the three participating sites. All homes had been recruited before randomisation. The constraint ensured an approximately equal distribution of the number of interventions to each geographic location. The randomisation system was held at NWORTH and has been coded and validated in R (statistical package) (36). Selection bias was reduced by inclusion of all participants identified as eligible and consented. Homes were approached in the order of appearance on the randomised list.

Sample size

The primary outcome was reduction of antipsychotics. It was estimated that about 30% of residents with dementia living in care homes were receiving antipsychotics, based upon best available data. We estimated that this proportion would be reduced to 10% for residents receiving Antipsychotic Review.

Based on PASS 11 (power analysis and sample size software), sample sizes of 96 in each group gives 82% power to detect a difference between the two proportions of -0.20. The test statistic used is the two-sided Z test to compare two independent proportions for a cluster randomised trial where the intra-cluster correlation is assumed to be 0.05. The significance level of the test is 0.05. After adjusting for a drop-out rate of 25%, the sample size required was 128 per arm, or about 16 participants per home. Based upon the effect size (>0.50) seen in the CADRES study, the study was designed to detect an effect size of 0.5 for the other outcomes. A total of 128 patients for each of the group comparisons gives 80% power to detect a treatment difference at a two-sided 0.05 significance level, if the true effect size is 0.5. Cluster randomisation reduces efficiency and leads to loss of power but was essential as the intervention has to be implemented throughout individual care homes. The design effect, otherwise known as the inflation factor (IF), is defined as the ratio of the total number of patients required using cluster randomisation to the number required using individual randomisation. Statistical theory leads to the following formula: DE = 1 + [(m - 1) □ r1] where r1= s2b/(s2b +s2w) called the intracluster correlation coefficient (ICC), where s2b is the between cluster variance and s2w is the within cluster variance. ICCs for authentic resident outcome measures (rather than process outcomes) rarely exceed 0.03. An estimated average of 16 eligible participants per cluster leads to an inflation factor of 1.45. Therefore 186 partipants were required to give this level of power for each outcome. Given the frailty of the population and the estimated mortality rate a total sample size of 240 was stipulated to allow for mortality and drop-out. This sample size does not give power to correct for multiple testing with respect to the three primary hypotheses.

Statistical analysis

The primary hypotheses were that in comparison to Person-Centred Care alone AR would lead to a greater reduction in antipsychotic use, SI would improve agitation and Exercise would reduce depression at the individual resident level. Analyses accounted for intervention, baseline demographic and clinical characteristics and site as covariates and exposure variables. All continuous outcome measures were scored using a 20% missing rule. Analysis used multiple linear regression models for continuous outcome measures and logistic

regression models for binary outcome measures. Robust standard errors were used throughout to account for clustering effects (37-39).

The primary outcome analysis was an Intention to treat analysis. For the main analysis age, gender and severity of dementia were included as covariates when modelling the five outcome measures. Site was also included as a stratification variable. For antipsychotic drug use and NPI-NH total score the corresponding baseline measures were also covariates. For each outcome, a model was fitted consisting of the baseline and all three interventions simultaneously to reflect the nature of a factorial design. When significant interaction effects were identified, these were included in linear models. Throughout, FAST and CDR scores were modelled as linear effects as they are naturally ordered. This reduced the degree of freedom and increased the statistical power. A p-value of 0.05 was adopted. Analyses were conducted using Stata version 13.

The primary analyses were treatment as allocated for all individuals with outcome data. In sensitivity analyses, a re-analysis was undertaken allocating the one care home that withdrew and did not receive any intervention as if they were allocated to the Person-Centred Care only group. For the main analysis only participants with follow-up data were included. Two further sensitivity analyses were undertaken imputing data for participants who had died or withdrawn using best and worst case scenario assumptions for missing data. In the worst case scenario CMAI or NPI-NH total score for all deaths were imputed as the maximum score in the corresponding care homes. For all those lost to follow-up or those who completed the follow up, but with the corresponding outcome measures missing, they were imputed as the mean score in the corresponding care homes. For antipsychotic use, all participants missing on their follow-up drug status were imputed as taking drugs. In the best case scenario the CMAI or NPI-NH total score for all deaths were imputed as the mean score in the corresponding care homes. For all those lost to follow-up or those who completed the follow-up, but where the corresponding outcome measures missing, these were imputed as the minimum score in the corresponding care homes. For antipsychotic use, all participants missing their follow-up drug status were imputed as not on antipsychotics.

Results

Cohort characteristics

Sixteen nursing homes were recruited and randomised between August and December 2011, and 277 participants randomised, of whom 195 (70%) completed the study. One home

withdrew after randomisation but before commencement of the intervention. Outcome measures on 12 of 21 participants from this home were collected at nine months. Flow of participants through the study is summarised in Figure 2.

Participants had a mean age of 85.26 (SD 7.02) and 74% were female. CDR scores were 12% mild, 40% moderate and 47% severe. FAST categories were 11% mild, 6% moderate, 64% moderately severe and 19% severe. 49 participants (18%) were taking antipsychotics, with no significant differences between AR and non-AR groups. Baseline characteristics are described fully in Table 1. The intra-home correlation coefficient for NPI-NH total score at baseline was 0.05. This is modest, suggesting that the clustering effect should not be overly influential in relation to the outcomes.

There was no significant difference in the total NPI-NH score or CMAI at baseline between non-completers and those completers in either people receiving (NPI-NH:-1.82, 95% CI -7.79 to 4.15, p=0.53; CMAI: -3.37, 95% CI -8.54 to 1.80, p=0.18) or not receiving the AR intervention (NPI-NH: 0.59, 95% CI -6.20 to 7.38, p=0.86; CMAI: -6.46, 95% CI -14.24 to 1.31, p=0.10).

Primary outcomes

Twenty of 118 (17%) people were receiving antipsychotics at baseline in the clusters receiving review. Twenty of 99 people (20%) were receiving antipsychotics at baseline in non-Antipsychotic Review clusters. Ten of the 20 (50%) people taking antipsychotics in the Antipsychotic Review group stopped antipsychotics before follow-up, but none of the individuals taking antipsychotics stopped treatment in the non-Antipsychotic Review group. Three people started antipsychotics in each group (<4%). Overall there was a significant reduction in antipsychotic use in the Antipsychotic Review group compared to the non-Antipsychotic Review group (OR 0.17, 95% CI 0.05 to 0.60, p=0.006). In addition there were no prescriptions of typical antipsychotics in the Antipsychotic Review care homes at follow-up. The doses used were similar at baseline and follow-up in both groups. The details of individual antipsychotic use at baseline and follow-up in the Antipsychotic Review homes are shown in more detail in Table 2. All of the participants for whom antipsychotics were discontinued in the Antipsychotic Review group had been on antipsychotics for at least three months at baseline, and therefore all individuals were eligible for discontinuation based upon the recommendations within the educational package. Additional caution was recommended for individuals with baseline NPI scores >14 based on previous randomised controlled trial

evidence (29). Only three of the discontinued patients had NPI scores over this threshold, although of note they had a mean deterioration of >20 points on the NPI.

Social Interaction did not confer any improvement in agitation, with a non-significant 4.96 disadvantage compared to Person-Centred Care alone (95% CI -1.33 to 11.25, P=0.113). Exercise conferred significant benefit with respect to depression (Mean difference -3.41, 95% CI 0.56 to 6.72 p=0.022) .Results of the full analysis are described in Table 3.

Secondary outcome measure: Mortality

After adjusting for baseline covariates the proportion of people dying in the group receiving neither Antipsychotic Review nor Social Interaction was 35%. This was reduced to 28% in the group receiving Antipsychotic Review but not Social Interaction and 19% in the group receiving both Antipsychotic Review and Social Interaction. The adjusted main analysis for mortality showed a significant interaction effect between Antipsychotic Review and Social Interaction (OR 2.06, 95% CI 1.06-4.01, P=0.033). In this main analysis model which included the baseline covariates, Antipsychotic Review, Social Interaction and Exercise and the interaction between Antipsychotic Review and Social Interaction, Antipsychotic Review conferred a non-significant reduction in mortality in the non-Social Interaction group (OR 0.67 95% CI 0.39-1.14 P=0.14). The variable impacting on reduced mortality in this model was Social Interaction (OR 0.26 95% CI 0.13 to 0.51, P<0.001). Exercise did not significantly contribute to mortality (OR 1.18 95% CI 0.71 to 1.98, P=0.522) (Table 3). A further analysis focusing specifically on the contrast between those receiving Antipsychotic Review and Social Interaction and those receiving neither demonstrated that the group receiving both Antipsychotic Review and Social Interaction had significantly reduced mortality compared to the group receiving neither (OR=0.36, 95% CI 0.23 to 0.57, p<0.001).

Secondary outcome measure: Neuropsychiatric symptoms

The Antipsychotic Review group had a non-significant disadvantage on the NPI-NH of 3.27 points (95% CI -0.54 to 7.07, p= 0.087) compared to the non-AR group. There was a significant interaction between Antipsychotic Review and Social Interaction (-7.81 95% CI -14.74 to -0.88) and after accounting for interactions, the group receiving Antipsychotic Review but not Social Interaction had a 7.37 point (95% CI 1.53 to 13.22, p=0.017) disadvantage compared to the group receiving neither Antipsychotic Review nor Social Interaction. Importantly, the disadvantage of AR on NPI-NH disappeared for the group receiving Antipsychotic Review and Social Interaction in comparison to patients not receiving Antipsychotic Review (-0.44, 95% CI -4.39 to 3.52, p=0.82). Exercise conferred a significant benefit with respect to NPI-NH score

(-4.01, 95% CI -7.91 to 0.10, p=0.045), but did not have a significant interaction effect with Antipsychotic Review. For the CMAI, there was no significant difference between the Antipsychotic Review and non- Antipsychotic Review groups (4.60, 95% CI -1.43 to 10.63, p=0.125) (Table 3).

Sensitivity Analysis

An additional analysis was performed to re-allocate the care home which did not implement any of the four interventions to the Person-Centred Care only group. The effect estimates became 0.25 (95% CI 0.07 to 0.91, p=0.035) for the impact of Antipsychotic Review on reduction of antipsychotic drugs. The interaction effects between Antipsychotic Review and Social Interaction intervention became 1.83 (95% CI 0.93 to 3.57, p=0.078) for mortality and -7.57 (95% CI -14.31 to -0.83, p=0.03) for NPI-NH score.

The two additional sensitivity analyses imputing data using best and worst case scenarios produced results that were consistent with the main analysis both numerically and in terms of statistical significance (Table 4). The only difference was that Exercise did not quite confer a statistically significant benefit on depression in one of the two sensitivity analysis (p=0.057).

Discussion

This 'real world' intervention focussed on training or primary care physicians and nursing home staff with support tools to reinforce best practice guidelines. The intervention significantly reduced antipsychotic use in people with dementia by 50%, even in a population with a baseline antipsychotic use below 20%. Descriptive data also indicated that there were no patients on typical antipsychotics at follow-up in the AR group. Exercise conferred significant benefits in depression and overall neuropsychiatric symptoms, but Social Interaction did not improve either agitation or total neuropsychiatric symptoms. In addition, the group receiving Antipsychotic Review in combination with Social Interaction had a significant reduction in mortality. However, compared to the non- Antipsychotic Review group, those receiving Antipsychotic Review experienced a significantly worse outcome on overall neuropsychiatric symptoms. Importantly, this impact was mitigated by the concurrent delivery of Social Interaction, and the group receiving Antipsychotic Review and Social Interaction had no deterioration in their NPI-NH score. These results strongly indicate that whilst substantial reductions in antipsychotics can be achieved using this 'real world' approach, that current best practice guidelines may not be achieving the best outcomes for people with dementia unless

effective non-pharmacological interventions are implemented alongside review of antipsychotics. Importantly, combining Antipsychotic Review with Social Interaction significantly reduced antipsychotic use and mortality without a worsening of neuropsychiatric symptoms and Exercise improved both neuropsychiatric symptoms and depression.

The detrimental impact of Antipsychotic Review on neuropsychiatric symptoms is an important finding and can likely be explained by the changed landscape of antipsychotic prescribing which is evident in recent international studies and in this cohort (23-25, 40). The Antipsychotic Review intervention was based on guidance created before the substantial reductions in antipsychotic use that have occurred over the last five years (10). Whilst this has achieved significant benefits it has meant that the severity of neuropsychiatric symptoms in people who are now receiving antipsychotics is likely to be much higher compared to previously. The finding indicates the urgent need for revision of guidelines, and in particular the need for a greater emphasis on the importance of providing evidence-based non-pharmacological interventions in conjunction with Antipsychotic Review to achieve overall benefits.

Interestingly, the negative impact of Antipsychotic Review on neuropsychiatric symptoms was not mitigated by Person-Centred Care but was mitigated by the addition of Social Interaction. This is difficult to interpret as the Social Interaction intervention on its own was actually associated with a non-significant worsening of neuropsychiatric symptoms, but is probably explained by the numerical reduction of antipsychotics in the nursing homes receiving Social Interaction. It is also possible that the mitigating benefits of Social Interaction were related to the specific use of Social Interaction as a therapeutic approach during antipsychotic withdrawal. The experience of therapists was that although care home staff were able to gather life story information they found it difficult to develop and maintain tailored plans or interventions resulting from this information based on Person-Centred Care alone. The Person-Centred Care intervention was based largely on understanding the underlying principles of Person-Centred Care and life story of individuals without further specified methods of applying this to improve communication, care planning and management of neuropsychiatric symptoms Whilst those receiving Person-Centred Care alone had support from the therapist to devise plans, the addition of more structured Social Interaction or Exercise provided this framework which appears to have made implementation more straightforward. .

The approach for reviewing antipsychotics was based on primary care education and on implementing processes within the care homes to prompt primary care review. The advantage

of this approach is that it did not require direct involvement of researchers or specialists in the review process, and would therefore be more feasible to implement in routine practice where many individuals are not under specialist care. As a result, the decision-making process that followed antipsychotic review, including further monitoring and ongoing treatment decisions, was not protocolized, but was based on the clinical judgement of the physicians informed by the educational input and best practice toolkit. It is therefore possible that some of the clinical decision making was not optimal, and this could have contributed to some of the worsening of neuropsychiatric symptoms associated with Antipsychotic Review. In addition, as this review was completed as part of clinical practice there was no routinely documented information regarding the reasons for changes or clinical decisions. It is of note that it was unusual for participants to be started on antipsychotics whether or not the primary care physicians received the educational Antipsychotic Review intervention, but that 50% of people receiving antipsychotics were discontinued In the Antipsychotic Review treatment arm, and that no patients remained on typical antipsychotics at follow-up in this group. In addition it is of note that all patients who were discontinued from antipsychotics in the Antipsychotic Review group had been prescribed an antipsychotic for more than three months at baseline and therefore met the recommended criteria for a trial discontinuation. In addition only three of the participants discontinued from antipsychotics had NPI scores >14, although these individuals have a mean deterioration on the total NPI of >20 points. These descriptive data indicate that Antipsychotic Review did follow the evidence-based principles outlined in the educational package. Although anecdotal, the descriptive data do further support the need for caution in discontinuing antipsychotics in people with NPI scores >14..

Also of note, the Exercise intervention, significantly improved neuropsychiatric symptoms and depression, consistent with previous literature (41, 42). Both interventions were based on enhancing positive personalised activities, and carry a common theme of Person-Centred Care as a core part of the interventions (15, 19). Both involved just 60 minutes of activity each week, providing feasible approaches for use in practice and to avoid worsening of symptoms during antipsychotic withdrawal.

The mortality figures also have important implications, particularly since mortality risk has been a key driver in the campaign to reduce antipsychotic use (9). Although Antipsychotic Review alone reduced mortality by >30%, this only became statistically significant in combination with Social Interaction. The reduction in mortality with Antipsychotic Review alone is valuable since it goes some way to validating the arguments put forward for continuous review in practice. However, this finding indicates the importance of a multi-faceted non-pharmacological

approach to care within a Person-Centred Care framework, highlighting the need for social engagement of individuals in a tailored way to improve clinical outcomes.

This study has many strengths and represents a robust evaluation of enhanced Person-Centred Care as an intervention for nursing homes. The study also had excellent retention of surviving participants. The intervention design followed best practice guidelines for Antipsychotic Review and published approaches for Social Interaction and Person-Centred Care with established benefits in this patient group. It is the first study to robustly evaluate a practical intervention that can be easily disseminated and implemented in routine clinical practice. The study demonstrated the clear utility of this approach in reducing antipsychotics in people with dementia living in nursing homes. There were also limitations. As the antipsychotic review was based on real life practice following an educational review it was not protocolized. In addition, although the study was adequately powered to examine each of the primary outcome measures, there was inadequate power to correct for testing three separate primary outcomes, which must be considered in the interpretation of the results.

Overall the study clearly demonstrates the feasibility of a real world intervention to reduce antipsychotic use in people with dementia, but highlights an urgent need to review current best practice guideless to ensure that review of antipsychotics is in the best interests of people with dementia. Updated guidance will also need to strongly emphasise the importance of evidence-based non-pharmacological interventions. Our study suggests that focussed intervention to promote social engagement is an important component of combined interventions to enable effective antipsychotic discontinuation and clinical outcomes.

Contributor Statement

This manuscript is submitted on behalf of the WHELD Investigators: Joanna Murray, Vanessa Lawrence, Renee Romeo, Martin Knapp, Apricot Hulse, Byron Cresse, Nicola Ferreria, Michaela Litchmore Dunbar, Claire Burley, Georgina Hughes, Jasmin Patel, Azucena Guzman Garcia and Astrid Schepers.

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Transparency Declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of this study. No important aspects of the study have been omitted. Any discrepancies from the study as planned have been explained.

Figures

Figure 1 Diagram of the factorial design of the study

Figure 2 CONSORT diagram showing flow of participants through the study

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Table 1: Table 1 Baseline demographic characteristics of residents by whether or not on antipsychotic review

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Characteristic	Antipsychotic review		Not on antipsychotic review		All	
	N	**%**	**N**	**%**	**N**	**%**
Total	146	100	131	100	277	100
Categorical variables						
Sex						
Female	110	75.34	95	72.52	205	74.01
Male	36	24.66	36	27.48	72	25.99
Ethnicity						
White	132	90.41	115	87.79	247	89.17
Other	12	8.22	16	12.21	28	10.11
Missing	2	1.37	0	0.00	2	0.72
Taking antipsychotics						
On drug	26	17.81	23	17.56	49	17.69
Not on drug	118	80.82	106	80.92	224	80.87
Missing	2	1.37	2	1.53	4	1.44
CDR Score						
Mild	20	13.70	14	10.67	34	12.27
Moderate	59	40.41	53	40.46	112	40.43
Severe	67	45.89	64	48.85	131	47.29
FAST Score						
Mild	19	13.01	11	8.40	30	10.83
Moderate	8	5.48	8	6.11	16	5.78
Moderately Severe	93	63.70	84	64.12	177	63.90
Severe	26	17.81	28	21.27	54	19.49
Continuous variables						
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age at assessment (years)	85.28	7.03	85.24	7.04	85.26	7.02
CMAI total score*	47.60	16.39	49.14	17.99	48.33	17.15

Total NPI-NH score (10 domains)†	13.21	14.60	16.02	15.72	14.54	15.18

*Data missing for one in each intervention group. † Data missing for one in each intervention group. N, total number of observations in the corresponding category. SD, standard deviation.

Table 2 Change in Antipsychotic Use between Baseline and Follow-up in the Antipsychotic Review Group

Baseline				**Follow-up**		
Drug	**N**	**Dose**	**Median dose**	**N**	**Dose**	**Median dose**
Quetiapine	10	25-150mg	75 mg	8	25-150mg	50 mg
Olanzapine	2	2.5-5mg	3.7 mg	1	5mg	
risperidone	4	0.5-1.5mg	1 mg	2	0.5-1.5mg	1 mg
Haloperidol	2	0.125-0.5mg	0.31 mg	0		
Amisulpiride	2	50-200mg	125 mg	2	100-200mg	150 mg

Word count: 3388
Tables: 4
Figures: 2

Table 3: Mean score or number at baseline and/or follow up along with the associated changes from baseline to follow up for completers by interventions based on raw scores and the adjusted mean differences for:

(a) Neuropsychiatric Symptoms (CMAI) (n = 194)

	Statistic	**Antipsychotic Review** (n=106)	**Not on Antipsychotic Review** (n=88)	**Social Interaction** (n=100)	**Not on Social Interaction** (n=94)	**Exercise** (n=93)	**Not on Exercis** (n=101)
Baseline	Mean	46.54	47.06	47.91	45.57	46.36	47.16
	SD	15.97	15.87	16.74	14.92	16.72	15.15
Follow-up	Mean	49.10	46.16	50.75	44.60	46.94	48.53
	SD	20.14	18.17	21.77	15.72	19.75	18.90
Change from baseline to follow up	Mean	2.56	-0.90	2.84	-0.97	0.58	1.37
	SD	18.29	17.89	19.32	16.68	18.08	18.29
Unadjusted difference between groups	Mean	3.46		3.81		-0.79	
	SD	25.58		25.52		25.72	
Adjusted difference between groups *	Mean	4.6		4.96		-1.76	
	SD	19.62		20.53		16.56	

(b) Neuropsychiatric Symptoms (NPI-NH) (n = 193)

	Statistic	**Antipsychotic Review** (n=106)	**Not on Antipsychotic Review** (n=87)	**Social Interaction** (n=100)	**Not on Social Interaction** (n=93)	**Exercise** (n=92)	**Not on Exercis** (n=101)
Baseline	Mean	12.52	15.93	15.05	12.99	12.02	15.92
	SD	13.89	15.96	15.51	14.25	14.78	14.87
Follow-up	Mean	14.62	13.05	14.89	12.86	11.73	15.90
	SD	13.36	11.13	12.35	12.43	10.84	13.41
Change from baseline to follow up	Mean	2.10	-2.88	-0.16	-0.13	-0.29	-0.01
	SD	17.16	15.64	15.63	17.74	14.94	18.12
Unadjusted difference between groups	Mean	4.98		-0.03		-0.28	
	SD	23.21		23.64		23.48	
Adjusted difference	Mean	7.37		5.45		-3.59	
	SD	13.04		11.60		11.38	

between groups *				

(c) CSDD Score (n = 178)

	Statistic	**Antipsychotic Review (n=98)**	**Not on Antipsychotic Review (n=80)**	**Social Interaction (n=88)**	**Not on Social Interaction (n=90)**	**Exercise (n=83)**	**Not on Exercis (n=95)**
Baseline	Mean	3.96	5.24	4.86	4.22	4.16	4.87
	SD	3.58	4.47	3.94	4.14	3.48	4.48
Follow-up	Mean	4.65	4.56	5.43	3.81	5.15	4.14
	SD	4.48	4.71	4.60	4.42	4.59	4.52
Change from baseline to follow up	Mean	0.68	-0.68	0.57	-0.42	0.99	-0.73
	SD	5.30	5.22	4.79	5.73	5.08	5.37
Unadjusted difference between groups	Mean	1.36		0.99		1.72	
	SD	7.44		7.47		7.39	
Adjusted difference between groups *	Mean	-1.70		1.15		-1.21	
	SD	5.85		6.20		6.62	

(d) Antipsychotic Use (n = 217)

	Statistic	**Antipsychotic Review** (n=118)	**Not on Antipsychotic Review** (n=99)	**Social Interaction** (n=110)	**Not on Social Interaction** (n=107)	**Exercise** (n=104)	**Not on Exercis** (n=113)
Baseline	Number	20	20	9	31	24	16
	%	16.95	20.20	8.18	28.97	23.08	14.16
Follow-up	Number	13	23	9	27	21	15
	%	11.02	23.23	8.18	25.23	20.19	13.27
Change from baseline to follow up	Number	-7	3	0	-4	-3	-1
	%	5.93	3.03	0.00	3.74	2.89	0.89
Unadjusted difference between groups	Number	0.41		0.26		1.65	
	%	16.25		20.48		15.22	

Adjusted difference between groups *	Number	0.17	0.60	1.31
	%	117.82	77.11	119.51

(e) Mortality (n = 255)

	Statistic	**Antipsychotic Review** (n=133)	**Not on Antipsychotic Review** (n=122)	**Social Interaction** (n=125)	**Not on Social Interaction** (n=130)	**Exercise** (n=122)	**Not on Exercis** (n=133)
Number of deaths	Number	26	34	25	35	29	31
	%	19.55	27.87	20.00	26.92	23.77	23.31
Unadjusted difference between groups	Number	0.63		0.68		1.03	
	%	10.95		10.97		10.95	
Adjusted difference between groups *	Number	0.67		0.26		1.18	
	%	4.66		6.90		5.34	

Table 4 Effect estimates for the three interventions and the interactions between interventions (where appropriate) based on the multiple linear or logistic regression models for the five outcome measures (complete case analyses)[*]

Continuous Outcomes			
	Mean difference	**P-values**	**95% CI**
CMAI score (n=194)			
Antipsychotic Review	4.60	0.125	-1.43 to 10.63
Social Interaction	4.96	0.113	-1.33 to 11.25
Exercise	-1.76	0.469	-6.83 to 3.30
CSDD (n=178)			
Antipsychotic Review	-1.70	0.183	-4.29 to 0.90
Social Interaction	1.15	0.235	-0.84 to 3.14
Exercise	-1.21	0.425	-4.35 to 1.93
Interaction Effect AR#EX[†]	4.65	0.015	1.03 to 8.27
NPI-NH total score (n=193)			
Antipsychotic Review	7.37	0.017	1.53 to 13.22
Social Interaction	5.45	0.046	0.12 to 10.77
Exercise	-3.59	0.045	-7.08 to -0.09
Interaction Effect AR#SI	-7.81	0.030	-14.74 to -0.88
Binary Outcomes			
	Odds Ratio	**P-values**	**95% CI**
Antipsychotic use (n=217)			
Antipsychotic Review	0.17	0.006	0.05 to 0.60
Social Interaction	0.60	0.393	0.19 to 1.93
Exercise	1.31	0.679	0.37 to 4.64
Death (n=255)			
Antipsychotic Review	0.67	0.141	0.39 to 1.14
Social Interaction	0.26	<0.001	0.13 to 0.51

Exercise	1.18	0.436	0.78 to 1.79
Interaction Effect AR#SI	2.06	0.033	1.06 to 4.01

*All models are adjusted for age, gender, study site, FAST score, CDR score and the corresponding baseline outcome measures; in addition, all models are adjusted for the 16 care home clusters to account for the clustered data structure. n is the total number of observations used in each model.

For the variables where interaction effects were included in the final analysis model, the differences between the analysis model just accounting for baseline covariates and the model including interaction effects is shown in Supplementary Table 1.

Supplementary Table 1: Sensitivity analyses based on the worst and best case data scenarios

Worst Case Scenario				
	Score	**Odds Ratio**	**P value**	**95% CI**
Antipsychotic Use (n = 273)				
Antipsychotic Review	**-**	**0.53**	**0.039**	**0.29 to 0.97**
Social Interaction	-	0.50	0.012	0.29 to 0.85
Exercise	-	1.53	0.163	0.84 to 2.79
CMAI (n = 275)				
Antipsychotic Review	7.37	-	0.102	-1.64 to 16.38
Social Interaction	4.21	-	0.301	-4.18 to 12.60
Exercise	-2.79	-	(0.392)	-9.52 to 3.95
CSDD (n = 275)				
Antipsychotic Review	0.71	-	0.603	2.13 to 3.55
Social Interaction	3.61	-	0.126	1.14 to 8.36
Exercise	**4.74**	-	**0.023**	**0.76 to 8.72**
Death (n = 277)				
Antipsychotic Review	-	0.68	0.153	0.40 to 1.16
Social Interaction	-	**0.40**	**0.024**	**0.18 to 0.89**
Exercise	-	1.24	0.378	0.77 to 2.00
NPI-NH (n = 275)				
Antipsychotic Review	9.09	-	0.045	0.21 to 17.96
Social Interaction	3.99	-	0.206	-2.45 to 10.43
Exercise	**-5.34**	-	**0.033**	-10.18 to -0.51
Best Case Scenario				
	Score	**Odds Ratio**	**P value**	**95% CI**
Antipsychotic Use (n =)				
Antipsychotic Review	**-**	**0.21**	**0.004**	**0.07 to 0.60**
Social Interaction	-	0.48	0.170	0.17 to 1.37

Exercise	-	1.44	0.483	0.52 to 3.94
CMAI (n = 194)				
Antipsychotic Review	5.15	-	0.115	-1.40 to 11.69
Social Interaction	5.18	-	0.112	-1.36 to 11.72
Exercise	-1.61	-	0.527	-6.91 to 3.69
CSDD (n = 194)				
Antipsychotic Review	0.47	-	0.621	-1.51 to 2.45
Social Interaction	2.75	-	0.115	-0.75 to 6.25
Exercise	2.64	-	(0.057)	-0.09 to 5.36
Death (n = 255)				
Antipsychotic Review	-	0.59	0.066	0.34 to 1.04
Social Interaction	-	**0.27**	**<0.001**	**0.14 to 0.52**
Exercise	-	1.18	0.447	0.77 to 1.81
NPI-NH (n = 193)				
Antipsychotic Review	6.60	-	0.025	0.97 to 12.24
Social Interaction	5.10	-	0.082	-0.73 to 10.92
Exercise	-3.74	-	0.049	-7.45 to -0.03

Supplementary Table 2: Comparison of Model including baseline covariates and interaction effects compared to the model just adjusting for baseline covariates when significant interaction effects were present

	Adjusted for Baseline Covariates And Interaction effects			Adjusted for only baseline covariates		
Continuous Outcomes						
	Mean Diff	**P-value**	**95% CI**	**Mean Diff**	**P-value**	**95% CI**
CSDD (n=178)						
Antipsychotic Review	-1.70	0.183	-4.29 to 0.90	1.43	0.201	-0.85 to 3.71
Exercise	-1.21	0.425	-4.35 to 1.93	-3.41	0.022	-6.72 to -0.56
Antipsychotic Review # Exercise	4.65	0.015	1.03 to 8.27	-	-	-
NPI-NH total score (n=193)						
Antipsychotic Review	7.37	0.017	1.53 to 13.22	3.27	0.087	-0.54 to 7.07
Social Interaction	5.45	0.046	0.12 to 10.77	1.46	0.482	-2.86 to 5.78
Antipsychotic Review # Social Interaction	-7.81	0.030	-14.74 to -0.88	-	-	-
Binary Outcomes						
	Odds Ratio	**P-values**	**95% CI**	**Odds Ratio**	**p-values**	**95% CI**
Death (n=255)						
Antipsychotic Review	0.67	0.141	0.39 to 1.14	0.93	0.739	0.62 to 1.41
Social Interaction	0.26	<0.001	0.13 to 0.51	0.37	0.001	**0.21 to 0.66**
Antipsychotic Review # Social Interaction	2.06	0.033	1.06 to 4.01	-	-	-

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