Impact of antipsychotic review and non-pharmacological intervention on health-related quality of life in people with dementia living in care homes: WHELD - A factorial cluster randomised controlled trial

Running head: Impact of WHELD on quality of life in people with dementia

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Key points

- Very few published studies have examined the impact of interventions on health-related quality of life (HRQL) for people with dementia, particularly in care home settings, despite the global importance of this outcome
- Antipsychotic review and withdrawal in people with dementia in care homes led to detrimental impact on HRQL
- Social Interaction mitigates the negative impacts of antipsychotic review
- It is essential to take a judicious approach to antipsychotic withdrawal, and prescribers should consider the use of Social Interaction interventions delivered by care staff to reduce the risk of harm

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Abstract

Background: Very few interventional studies have directly examined the impact of treatment approaches on Health-Related Quality of Life (HRQL) in people with dementia. This is of particular importance in therapies to address behavioural symptoms, where HRQL is often severely affected.

Methods: Analysis within the WHELD cluster-randomised factorial study in 16 UK care homes examining the impact of person-centred care in combination with Antipsychotic Review, Social Interaction and Exercise interventions. This study analysed impact on HRQL through the DEMQOL-Proxy.

Results: Data on HRQL were available for 187 participants. People receiving Antipsychotic Review showed a significant worsening in two DEMQOL-Proxy domains (negative emotion: p=0.02; appearance: p=0.04). A best-case scenario analysis showed significant worsening for total DEMQOL proxy score. Social Interaction intervention resulted in a significant benefit to HRQL (p=0.04). There was no deterioration in HRQL in groups receiving both Antipsychotic Review and Social Interaction (p=0.62)

Conclusions: This demonstrates an important detrimental impact of discontinuation of antipsychotics in dementia on HRQL, highlighting the need for careful review of best practice guidelines regarding antipsychotic use, and emphasizing the importance of providing evidence-based non-pharmacological interventions in conjunction with antipsychotic review.

Introduction

Approximately one third of people with dementia reside in a care home, with up to 80% of residents having dementia (Corbett et al., 2013). Although the concept of personhood in dementia suggests that wellbeing and quality of life is achievable for all people with dementia given the right environment and person-centred support, most studies highlight major impairments in health-related quality of life (HRQL), particularly in care home settings.

The combination of cognitive, functional and communication impairment exerts a significant impact on HRQL and frequently leads to prescription of antipsychotic medication in these individuals. Meta-analyses of RCTs of atypical antipsychotics in people with Alzheimer's disease (AD) highlight modest benefit in the treatment of aggression and psychosis over periods of six to12 weeks (Ballard and Waite, 2006). However none of the eighteen RCTs included HRQL as an outcome. This is of particular importance because antipsychotics are associated with well-established safety concerns, including increased risk of mortality, accelerated cognitive decline, stroke, falls and sedation, all of which have the potential to impact negatively on HRQL (Ballard et al., 2011, Schneider et al., 2005, Ballard et al., 2009, Schneider et al., 2006, Corbett and Ballard, 2012). Secondary analysis from a previous trial of a person-centred care programme indicated an improvement in HRQL following discontinuation of antipsychotic medication (Fossey et al., 2006). More judicious use of antipsychotics has been heavily promoted in clinical practice in the past decade, leading to a decline in unnecessary prescriptions in the UK (Barnes et al., 2012). Within this changing landscape of antipsychotic use there is an urgent need for clarity on the role of antipsychotics in practice and their impact on HRQL in people with dementia.

There is increasingly robust evidence supporting the application of Person-centred care (PCC) principles and the use of non-pharmacological interventions for the management of neuropsychiatric symptoms. These approaches are prominent in best practice guidance (Chenoweth et al., 2009, Fossey et al., 2006, Fossey et al., 2014, Teri et al., 1997, Cohen-Mansfield et al., 2007, Moniz Cook et al., 2012). Of note however, whilst interventions focussing on PCC training have improved neuropsychiatric symptoms (Chenoweth et al., 2009) and reduced antipsychotic prescriptions (Fossey et al., 2006), they have not improved HRQL, except in the sub-group of individuals who discontinued antipsychotics (Fossey et al., 2006). A recent systematic review highlighted the benefit of non-pharmacological interventions using social interaction and pleasant activities, showing impact on both neuropsychiatric symptoms and antipsychotic use (Testad et al., 2014). Studies have also indicated the value of physical activity through personalized exercise interventions in improving neuropsychiatric symptoms (Teri et al., 2003). A key question is therefore whether PCC training approaches can be augmented by specific evidence-based non-pharmacological interventions. As non-pharmacologcial interventions are the main alternative to antipsychotics (Alzheimer's Society, 2012), it is also vital to understand the combined impact of antipsychotic review and non-pharmacological treatments to inform clincial practice.

There is an emerging consensus of the value in measuring broad patient-rated outcomes such as HRQL as well as discrete areas of function like cognition and behaviour in people with dementia (Banerjee, 2010, Whitehouse, 2000, Rabins et al., 2007). The DEMQOL system was developed to generate a robust disease-specific

measure of HRQL for dementia by using patient self-report and carer proxy report (Smith et al., 2007, Smith et al., 2005). DEMQOL-Proxy was developed from a conceptual framework that includes health and well-being, cognitive functioning, social relationships, daily activities, and self-concept (Smith et al., 2005). The system was developed for use across all types of dementias, care arrangements, and levels of severity. Psychometric analysis has shown it to be both reliable and valid. DEMQOL-Proxy has good psychometric performance in severe dementia as well as mild and moderate dementia.

The 'Improving Wellbeing and Health for People with Dementia' (WHELD) research programme aims to develop and evaluate an optimised antipsychotic review and person-centred care (PCC) intervention to reduce antipsychotic use and improve wellbeing for people with dementia in care homes. The study adopted a novel factorial design to examine the added impact of antipsychotic review, Social Interaction and personalized exercise respectively when combined with PCC training. This analysis of data from the WHELD RCT therefore sought to determine whether antipsychotic review, alone or in combination with evidence-based non-pharmacological approaches confers significant benefit to HRQL. The primary outcome of impact on neuropsychiatric symptoms is described in a previous publication (Ballard et al., 2016).

Method

Study design

Analysis of data from a cluster randomised, 2X2X2 factorial design RCT with two replications in 16 care homes in the UK 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 for nine months, in addition to training in PCC. Most homes were randomized to more than one of the three interventions (antipsychotic review, social intervention, personalised exercise) (Figure 1). The study received ethical approval from South-Central Oxford REC C (11/SC0066). The trial is registered 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

This study recruited people with dementia (Stage 1 or greater on the Clinical Dementia Rating Scale (Morris, 1993) and/or a score of 4 or greater on Functional Assessment Staging (FAST) (Reisberg, 1984)). Care homes had a 2013 Care Quality Commission rating of 'adequate' or better. Eight homes were selected from a convenience sample and another eight were selected randomly. Homes were excluded if less than 60% of residents had dementia or if the home was in receipt of local authority special support. All eligible residents were invited to participate. Baseline and follow-up data were collected on all residents who consented and met the inclusion criteria at each participating care home.

Consent for care home involvement was obtained from the care home manager. 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 PCC training intervention for nine months. Eight care homes were randomised to receive Antipsychotic Review. Eight homes were also randomised to Exercise and eight to Social Interaction following the factorial design (Figure 1). The interventions were delivered by a trained therapist. Therapists coordinated intervention delivery to 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 (PCC)

The PCC intervention was based on tools developed in the evidence-based Focussed Intervention for Training of Staff (FITS) manual, which has demonstrated efficacy in a RCT (Fossey et al., 2006). Additional evidence-based materials were included to provide a comprehensive training and implementation approach. The intervention had five main themes: (i) Creating an understanding of dementia and PCC; (ii) Enabling each care home to assess how staff deliver PCC; (iii) Recognising the relationship between an individuals' experience, behavior and wellbeing; (iv) Identifying how staff–resident interactions impact on the care experience; (v) Reviewing care planning and delivery based on these PCC principles. This training package was delivered to all available staff in participating homes.

Antipsychotic Review

Antipsychotic Review was based on NICE dementia guidelines and focussed specifically on review of antipsychotic prescriptions by primary care physicans or psychiatric specialists (National Institute for Health and Clinical Excellence (NICE), 2006). Review was guided by guidelines on the management of neuropsychiatric symptoms developed by Alzheimer's Society and the UK Department of Health (Alzheimer's Society, 2012). The intervention used the guidelines and additional supporting educational resources consistent with international best practice. WHELD therapists worked with champions and other staff to develop processes at their care home to prompt antipsychotic review. Therapists also worked with physicians and staff to augment PCC during antipsychotic withdrawal. The guidelines highlighted the need for careful medical assessment of the underlying causes of neuropsychiatric symptoms (such as pain and delirium), a first line approach of using non-drug interventions, the use of pharmacotherapy only in cases where symptoms were severe or causing risk, and the importance of regular review and monitoring of existing prescriptions. Care home staff were invited to training sessions focused on the need for safe antipsychotic prescribing and review and ways to engage with physicians. Physicians attended an interactive seminar and/or practice meeting to discuss the guidance and consider specific patient scenarios. The goal of the Antipsychotic Review intervention was to promote informed medication review. Prescribing decisions were made independently by the participants' own physician. In the majority of cases this was the person's primary care physician.

Social Interaction with Pleasant Activities

The Social Interaction intervention was based on three evidence based approaches - the Positive Events Schedule (Teri et al., 2008), Social Interaction intervention

(Cohen-Mansfield et al., 2012) and N.E.S.T programme (Buettner, 2009). with supplementary communications skills training for staff to assist in their use of the approaches with people with impaired communication. Individualised care plans were developed by incorporating information collected about individual's life histories and interests to ensure that activities were personalised. The Social Interaction intervention aimed to provide at least one hour a week of social interaction, or to increase social interaction by 20%.

Exercise

The Exercise intervention was based on two evidence-based protocols, the Seattle protocols (Teri et al., 2008) and N.E.S.T manual (Buettner, 2009). The aim was to promote physical activity, with a focus on pleasant experience to engage participants in at least one hour per week (or 20% more than at baseline). Individual Exercise plans were created by the therapist and champion according to the resident's interests, abilities and health status. Exercise plans usually included routine walking with additional activities such as seated or standing exercise to music, dancing or chair volleyball.

Outcome measures

HRQL as measured by DEMQOL-Proxy, was a secondary outcome measure in the RCT. The instrument consists of 31 items answered on a four point Likert scale (a lot/quite a bit/a little/not at all) and administered by an interviewer, blind to treatment allocation, using response cards. Items are scored from one to four, generating a total score between 31 and 124 with higher scores indicative of better HRQL. All items refer to the last week. DEMQOL-Proxy has acceptable content validity and

high levels of acceptability, reliability, and validity across the range of dementia severity. Further exploratory factor analysis carried out in an independent sample (Mulhern et al., 2012, Mulhern et al., 2013) derived a five-factor model explaining 49.3% of variance (cognition, negative emotion, daily activities, positive emotion, appearance). The main outcome of DEMQOL-Proxy is the total score which yields an assessment of global HRQL in dementia. To understand the effects observed, we also completed secondary data analyses at a domain level using the five factors identified above.

Antipsychotic and other psychotropic drugs were classified according to the British National Formulary. Assessments were carried out at baseline and nine months later by research assistants blind to intervention allocation.

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 location. The randomisation system was held at the Bangor Clinical Trials Unit (NWORTH) and has been coded and validated in the R statistical package (Russell et al., 2011). 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 study was powered to examine reduction in antipsychotic use (Ballard et al., 2016). HRQL was evaluated as a key exploratory outcome.

Statistical analysis

The main analysis included age, gender and severity of dementia as covariates. Site was also included as a stratification variable. For the evaluation of impact on HRQL, baseline DEMQOL-proxy score was included as a covariate. 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 main analyses were treatment as allocated for all individuals with outcome data. Sensitivity analyses included an intention-to-treat analysis, imputing data for best and worst case scenarios for individuals who died or did not complete follow-up assessments. For the main analysis only participants with follow-up data were included so the home that withdrew at randomisation was not included.

Results

Cohort characteristics

Sixteen care homes were recruited and randomised between August and December 2011, including 277 participants, 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 85.3 (SD 7.02) and 74% were female. CDR scores were 13% 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 at baseline, with no significant differences between Antipsychotic Review and non-Antipsychotic Review groups. Baseline characteristics are described fully in Table 1.

Effect of Antipsychotic Review

The impact of the Antipsychotic Review on antipsychotic use has been described in a parallel report (Ballard et al., 2016). To summarize, the intervention conferred a statistically significant 50% reduction in antipsychotic use in the Antipsychotic Review group compared to no reduction in the comparison group. There was also a statistically significant 30% reduction in mortality in the group receiving Antipsychotic Review and Social Interaction (Ballard et al., 2016).

Effect of Antipsychotic Review on HRQL

DEMQOL-Proxy scores were available for 187 residents at baseline and follow-up. Compared to people not receiving Antipsychotic Review, those receiving Antipsychotic Review showed a 4.54 (95% CI -9.26 to 0.19) point worsening (p=0.06) in their DEMQOL-Proxy scores which approached statistical significance. The worsening in HRQL was driven by a statistically significant worsening in the

negative emotion (mean difference -1.60, 95% CI -2.89 to -0.31); p=0.02) and appearance (mean difference -0.49; 95% CI -0.94 to -0.04, p=0.04) DEMQOL domains (Table 3). The results were similar in sensitivity analyses, but attained statistical significance for a worsening of total DEMQOL proxy in the best case scenario analysis (Supplementary Table 1)

Effect of non-pharmacological interventions on HRQL

A statistically significant six-point improvement in HRQL was seen in the group receiving Social interaction (Mean difference 6.04, 95% CI 0.24 to 11.84, p=0.04) compared to those not receiving this intervention.

Secondary analyses suggested that there were also HRQL improvements observed for Social Interaction in the cognition (mean difference 3.07, 95% CI 0.45 to 5.70, p=0.03) and appearance (mean difference 0.77; 95% CI 0.22 to 1.32, p=0.01) DEMQOL-proxy domains (Table 3). The sensitivity analyses showed similar benefits for social intervention on the total DEMQOL proxy, with slightly higher levels of statistical significance (Supplementary Table 1).

No impact on overall HRQL (DEMQOL total) was observed for the Exercise intervention in the main (Table 3) or sensitivity (Supplementary Table 1) analyses, although a significant benefit was seen for positive emotion (Mean difference 1.20, 95% CI 0.67-1.73, P<0.001)

There were no significant interaction effects between any of the interventions with respect to HQRL. However, importantly, there was no deterioration in HQRL in the

group receiving both Antipsychotic Review and Social Interaction compared to those receiving neither of these interventions (mean difference 1.23, 95% CI -3.88 TO 6..33, p=0.62), suggesting that reviewing antipsychotics in conjunction with the Social Interaction intervention enabled maintenance of HRQL in these individuals.

Discussion

The intervention evaluated in this study, which was designed to be fit-for-purpose for UK care homes, focussed on improving the HRQL of people with dementia in these settings by implementing best practice and evidence-based guidelines to review antipsychotics and utilise psychosocial interventions. The study has two main findings. Firstly, that contrary to our hypothesis the rigorous review of antipsychotic medication came at a cost in terms of worsening of HRQL by 4.54 points on the DEMQOL-Proxy (Cohen's d effect size 0.32) for those receiving the Antipsychotic Review intervention compared to those who did not. Secondly, that Social Interaction, in combination with PCC training, resulted in an improvement in HRQL for residents with dementia of 6.04 points (Cohen's d -0.51). The effect sizes observed in terms of change in HRQL exceed the thresholds that are used to define clinically meaningful benefit, and would be defined in established literature as a small to medium effect. They also compare favourably with Effect Sizes reported for other interventions with impact on HRQL(Cohen, 1988). Importantly however there was no deterioration in HQRL in the group receiving concurrent Antipsychotic Review and Social Interaction.

This is the first study to investigate the cost to HQRL of stopping antipsychotics through rigorous, evidence-based implementation of antipsychotic review. The

detrimental impact of Antipsychotic Review on HRQL is an important finding, and had not been anticipated. The data generated here are a unique contribution to this debate regarding antipsychotic use (Health & Social Care Information Centre, 2012, Barnes et al., 2012, Gallini et al., 2014, Centers for Medicare & Medicaid Services, 2013). The review protocol used in this study was based on guidance created before the substantial reductions in antipsychotic use that have occurred in the UK over the last five years. Whilst this has achieved significant benefits in terms of mortality and other adverse effects, it may also mean that the severity of neuropsychiatric symptoms in people receiving antipsychotics is likely to be higher than before. A halving of prescription rates and a reduction in mortality was achieved in this study (Ballard et al., 2016) but it may be that the pressure to discontinue these drugs meant that some who were benefiting from them were withdrawn, with a consequent increase in neuropsychiatric symptoms and reduction in HRQL (Banerjee et al., 2006). The debate on the use of antipsychotics in dementia is one that rapidly becomes polarised. However in the absence of other effective pharmacological treatments, these data underline the need for care when discontinuing these medications. In particular, the results highlight the importance of providing an evidence-based non-pharmacological intervention in combination with Antipsychotic Review since this appeared to mitigate the negative effects on HRQL.

Previous studies have shown that PCC training can reduce antipsychotics and improve neuropsychiatric symptoms, but has not demonstrated an impact on HRQL. Importantly, the findings from this study suggest that adding a simple, low intensity personalised social intervention to PCC training led to significant benefits in HRQL. The addition of enhancement of social interaction, with an emphasis on developing

care plans provided a concrete and comprehensible framework. This enabled staff to understand the principles of PCC and facilitated the integration of PCC into their caring role.

Improving HRQL, in addition to achieving specific goals or reducing specific symptoms or behaviours, should be a key objective of any intervention study in people with dementia and is also an essential component for analysing cost-effectiveness. This study demonstrates the utility and value of including a measure of HRQL such as DEMQOL in evaluations of interventions in complex conditions where success in achieving one goal comes at the cost of a decrease in HRQL unless supported by other non-pharmacological intervention.

This study has a number of strengths and weaknesses. It represents a robust evaluation of a simple and pragmatic enhanced PCC intervention for care homes. The study also had excellent retention of surviving participants. The intervention design followed best practice guidelines and focussed exclusively on interventions with established benefits in improving symptoms in this patient group. It is the first study to robustly evaluate a practical care home training intervention in HRQL terms that can be easily disseminated and implemented in routine clinical practice. There were also limitations. The study was powered as an exploratory study and did not adjust power to allow for three main analyses examining impact of interventions on HRQL which must be considered in the interpretation of the results. Furthermore, it is important to recognise that the DEMQOL-Proxy measure relies on observation of behaviour, meaning that behaviour change may lead to a change in score (Hoe et

al., 2006). However, the results were very consistent across a series of sensitivity analyses.

Conclusion

This RCT demonstrates an important detrimental impact of discontinuation of antipsychotics in dementia on proxy-rated HRQL. The results highlight the need for careful review of best practice guidelines regarding antipsychotic use, and emphasize the importance of providing evidence-based non-pharmacological interventions in conjunction with antipsychotic review and discontinuation. The study also provides clear evidence supporting the value of the WHELD intervention, combining Social Interaction with PCC as an effective approach to improve HRQL in people with dementia.

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Table 1 Baseline demographic characteristics of residents by whether or not on antipsychotic review. Values are numbers (percentages) or mean (SD) of

residents, n is the number of non-missing counts in the corresponding categories.

Characteristic	Antipsychotic review		Not on antipsychotic review		Total	
	N	%	N	%	N	%
Total	146	100	131	100	277	100
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
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age at assessment (years)	85.28	7.03	85.24	7.04	85.26	7.02
DEMQOL (proxy)[a]	105.95	9.29	102.23	14.96	104.21	12.38

[a]Data missing for three in Antipsychotic Review group and six in non-Antipsychotic Review group. *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: Mean quality of life score (SD) for people with dementia assessed by caregivers at baseline and follow up along with the associated mean changes (SD) from baseline to follow up and mean (SD) differences between groups for completers by interventions

Quality of life score for people with dementia (proxy) (n=187)	**Antipsychotic Review (n=105)**	**Not on Antipsychotic Review (n=82)**	**Social Interaction (n=95)**	**Not on Social Interaction(n=92)**	**Exercise (n=91)**	**Not on Exercise (n=96)**
Baseline	106.51 (9.14)	102.69 (15.22)	105.93 (12.67)	103.70 (11.86)	106.45 (11.77)	103.31 (12.65)
Follow up	102.11 (13.41)	105.79 (10.53)	106.84 (8.90)	100.51 (14.45)	103.85 (12.85)	103.61 (11.90)
Unadjusted mean change from baseline to follow up	-4.40 (15.12)	3.10 (14.77)	0.91 (13.02)	-3.19 (17.33)	-2.60 (15.74)	0.30 (14.99)
Unadjusted mean difference of the mean change from baseline to follow up between the two intervention groups	-7.5 (21.14)		4.1 (21.68)		-2.9 (21.74)	

Mean difference between the two intervention groups at follow-up adjusted using linear model	-4.54 (15.06)	6.04 (18.60)	-2.66 (18.18)

Table 3: Effect estimates for the three interventions for DEMQOL-proxy and the associated 5 sub-scales based on multiple linear regression models (complete case analyses)*

	Antipsychotic Review			**Social Interaction**			**Exercise**		
	Linear regression Coefficient	**P value**	**95% CI**	**Linear regression Coefficient**	**P value**	**95% CI**	**Linear regression Coefficient**	**P value**	**95% CI**
DEMQOL-proxy score (n=187)	-4.54	(0.059)	(-9.26 to 0.19)	**6.04**	**(0.042)**	**(0.24 to 11.84)**	-2.66	(0.334)	(-8.34 to 3.02)
Cognition sub-score (n=183)	-1.20	(0.284)	(-3.51 to 1.10)	**3.07**	**(0.025)**	**(0.45 to 5.70)**	-1.03	(0.394)	(-3.54 to 1.47)

Negative emotion sub-score (n=192)	**-1.60**	**(0.018)**	**(-2.89 to -0.31)**	-0.07	(0.924)	(-1.70 to 1.55)	-0.68	(0.378)	(-2.28 to 0.92)
Positive emotion sub-score (n=189)	0.14	(0.572)	(-0.36 to 0.64)	0.19	(0.458)	(-0.35 to 0.74)	**1.20**	**(<0.001)**	**(0.67 to 1.73)**
Daily activity sub-score (n=186)	-0.44	(0.050)	(-0.88 to 0.00)	0.33	(0.204)	(-0.20 to 0.86)	-0.28	(0.351)	(-0.89 to 0.34)
Appearance sub-score (n=188)	**-0.49**	**(0.035)**	**(-0.94 to -0.04)**	**0.77**	**(0.009)**	**(0.22 to 1.32)**	-0.30	(0.178)	(-0.74 to 0.15)

*Adjusted for age at baseline assessment, gender, study site, FAST score, CDR score and the corresponding baseline outcome measures. Standard errors were adjusted for the clustering effect of care homes. n is the total number of observations used in each model.

Supplementary Table 1: Sensitivity analyses based on the worst and best case data scenarios as defined for DEMQOL-proxy and the associated five sub-scales*

	Antipsychotic Review			**Social Interaction**			**Exercise**		
	Linear regression Coefficient	**P value**	**95% CI**	**Linear regression Coefficient**	**P value**	**95% CI**	**Linear regression Coefficient**	**P value**	**95% CI**
Worst Case Scenario									
DEMQOL-proxy score (n=268)	-5.28	0.124	-12.19 to 1.63	**9.93**	**0.008**	**2.95 to 16.90**	-0.65	0.842	-7.48 to 6.18
Cognition sub-score (n=264)	-1.88	0.280	-5.47 to 1.70	**4.89**	**0.013**	**1.20 to 8.58**	-0.50	0.785	-4.35 to 3.34

Negative emotion sub-score (n=272)	**-1.44**	**0.049**	**-2.88 to -0.006**	0.75	0.302	-0.74 to 2.24	-0.77	0.257	-2.16 to 0.62
Positive emotion sub-score (n=268)	0.19	0.338	-0.21 to 0.59	**0.42**	**0.044**	**0.01 to 0.83**	**1.13**	**<0.001**	**0.72 to 1.54**
Daily activity sub-score (n=267)	-0.89	0.137	-2.10 to 0.32	0.65	0.254	-0.52 to 1.82	-0.29	0.567	-1.33 to 0.76
Appearance sub-score (n=270)	-0.51	0.095	-1.12 to 0.10	1.31	0.002	0.59 to 2.03	-0.30	0.364	-0.98 to 0.38
Best Case Scenario									
DEMQOL-proxy score (n=268)	-4.55	0.048	-9.05 to -0.04	**6.09**	**0.034**	**0.54 to 11.65**	-2.27	0.399	-7.85 to 3.31
Cognition sub-score (n=264)	-1.29	0.234	-3.52 to 0.93	**3.00**	**0.028**	**0.38 to 5.62**	-1.29	0.319	-3.96 to 1.38
Negative emotion sub-	**-1.47**	**0.021**	**-2.68 to -**	0.002	0.998	-2.99 to	-0.54	0.437	-1.98 to

score (n=272)			**0.26**			0.28			0.90
Positive emotion sub-score (n=268)	0.10	0.796	-0.71 to 0.91	0.36	0.354	-0.44 to 1.16	**1.38**	**0.004**	**0.50 to 2.25**
Daily activity sub-score (n=267)	**-0.44**	**0.034**	**-0.85 to -0.04**	0.25	0.277	-0.22 to 0.71	-0.28	0.270	-0.80 to 0.24
Appearance sub-score (n=270)	**-0.47**	**0.034**	**-0.90 to -0.04**	**0.81**	**0.008**	**0.25 to 1.37**	-0.37	0.166	-0.92 to 0.17

*Adjusted for age at baseline assessment, gender, study site, FAST score, CDR score and the corresponding baseline outcome measures. Standard errors were adjusted for the clustering effect of care homes. n is the total number of observations used in each model.

Worst case scenario is the dataset where the DEMQOL Proxy scores for all deaths were imputed as the minimum score in the corresponding care homes and for all those lost to follow up or those completed the follow up but with the corresponding outcome measures missing were imputed as the mean score in the corresponding care homes. The best case scenario is the dataset where the DEMQOL Proxy scores for all deaths were imputed as the mean score in the corresponding care homes and for all those lost to

follow up or those completed the follow up but with the corresponding outcome measures missing were imputed as the maximum score in the corresponding care homes.

References

ALZHEIMER'S SOCIETY. 2012. *Optimising treatment and care for behavioural and psychological symptoms of dementia: A best practice guide* [Online]. Optimising treatment and care for behavioural and psychological symptoms of dementia: A best practice guide. [Accessed 23 April 2014].

BALLARD, C., CREESE, B., CORBETT, A. & AARSLAND, D. 2011. Atypical antipsychotics for the treatment of behavioral and psychological symptoms in dementia, with a particular focus on longer term outcomes and mortality. *Expert Opin Drug Saf,* 10**,** 35-43.

BALLARD, C., ORRELL, M., YONGZHONG, S., MONIZ-COOK, E., STAFFORD, J., WHITTAKER, R., WOODS, B., CORBETT, A., GARROD, L., KHAN, Z., WOODWARD-CARLTON, B., WENBORN, J. & FOSSEY, J. 2016. Impact of Antipsychotic Review and Nonpharmacological Intervention on Antipsychotic Use, Neuropsychiatric Symptoms, and Mortality in People With Dementia Living in Nursing Homes: A Factorial Cluster-Randomized Controlled Trial by the Well-Being and Health for People With Dementia (WHELD) Program. *Am J Psychiatry,* 173**,** 252-62.

BALLARD, C. & WAITE, J. 2006. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev***,** CD003476.

BALLARD, C. G., GAUTHIER, S., CUMMINGS, J. L., BRODATY, H., GROSSBERG, G. T., ROBERT, P. & LYKETSOS, C. G. 2009. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol,* 5**,** 245-55.

BANERJEE, S. 2010. Living well with dementia--development of the national dementia strategy for England. *Int J Geriatr Psychiatry,* 25**,** 917-22.

BANERJEE, S., SMITH, S. C., LAMPING, D. L., HARWOOD, R. H., FOLEY, B., SMITH, P., MURRAY, J., PRINCE, M., LEVIN, E., MANN, A. & KNAPP, M. 2006. Quality of life in dementia: more than just cognition. An analysis of associations with quality of life in dementia. *J Neurol Neurosurg Psychiatry,* 77**,** 146-8.

BARNES, T. R., BANERJEE, S., COLLINS, N., TRELOAR, A., MCINTYRE, S. M. & PATON, C. 2012. Antipsychotics in dementia: prevalence and quality of antipsychotic drug prescribing in UK mental health services. *Br J Psychiatry,* 201**,** 221-6.

BUETTNER, L., FITZSIMMONS, S 2009. *N.E.S.T Approach: Dementia Practice Guidelines for Disturbing Behaviours*, Venture Publishing, Inc.

CENTERS FOR MEDICARE & MEDICAID SERVICES. 2013. *Press release: New data show antipsychotic drug use is down in nursing homes nationwide* [Online]. http://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-Releases/2013-Press-Releases-Items/2013-08-27.html. [Accessed 17th September 2014].

CHENOWETH, L., KING, M. T., JEON, Y. H., BRODATY, H., STEIN-PARBURY, J., NORMAN, R., HAAS, M. & LUSCOMBE, G. 2009. Caring for Aged Dementia Care Resident Study (CADRES) of person-centred care, dementia-care mapping, and usual care in dementia: a cluster-randomised trial. *Lancet Neurol,* 8**,** 317-25.

COHEN-MANSFIELD, J., LIBIN, A. & MARX, M. S. 2007. Nonpharmacological treatment of agitation: a controlled trial of systematic individualized intervention. *J Gerontol A Biol Sci Med Sci,* 62**,** 908-16.

COHEN-MANSFIELD, J., THEIN, K., MARX, M. S., DAKHEEL-ALI, M. & FREEDMAN, L. 2012. Efficacy of nonpharmacologic interventions for agitation in advanced dementia: a randomized, placebo-controlled trial. *J Clin Psychiatry,* 73**,** 1255-61.

COHEN, J. 1988. *Statistical Power Analysis forthe Behavioural Sciences,* New Jersey, USA, Lawrence Erlbaum Associates.

CORBETT, A. & BALLARD, C. 2012. Antipsychotics and mortality in dementia. *Am J Psychiatry,* 169**,** 7-9.

CORBETT, A., NUNEZ, K. & THOMAS, A. 2013. Coping with dementia in care homes. *Maturitas,* 76**,** 3-4.

FOSSEY, J., BALLARD, C., JUSZCZAK, E., JAMES, I., ALDER, N., JACOBY, R. & HOWARD, R. 2006. Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. *BMJ,* 332**,** 756-61.

FOSSEY, J., MASSON, S., STAFFORD, J., LAWRENCE, V., CORBETT, A. & BALLARD, C. 2014. The disconnect between evidence and practice: a systematic review of person-centred interventions and training manuals for care home staff working with people with dementia. *Int J Geriatr Psychiatry,* 29**,** 797-807.

GALLINI, A., ANDRIEU, S., DONOHUE, J. M., OUMOUHOU, N., LAPEYRE-MESTRE, M. & GARDETTE, V. 2014. Trends in use of antipsychotics in elderly patients with dementia: Impact of national safety warnings. *Eur Neuropsychopharmacol,* 24**,** 95-104.

HEALTH & SOCIAL CARE INFORMATION CENTRE. 2012. *National Dementia and Antipsychotic Prescribing Audit* [Online]. http://www.hscic.gov.uk/dementiaaudit. [Accessed 8th September 2014].

HOE, J., HANCOCK, G., LIVINGSTON, G. & ORRELL, M. 2006. Quality of life of people with dementia in residential care homes. *Br J Psychiatry,* 188**,** 460-4.

MONIZ COOK, E. D., SWIFT, K., JAMES, I., MALOUF, R., DE VUGT, M. & VERHEY, F. 2012. Functional analysis-based interventions for challenging behaviour in dementia. *Cochrane Database Syst Rev,* 2**,** CD006929.

MORRIS, J. C. 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology,* 43**,** 2412-4.

MULHERN, B., ROWEN, D., BRAZIER, J., SMITH, S., ROMEO, R., TAIT, R., WATCHURST, C., CHUA, K. C., LOFTUS, V., YOUNG, T., LAMPING, D., KNAPP, M., HOWARD, R. & BANERJEE, S. 2013. Development of DEMQOL-U and DEMQOL-PROXY-U: generation of preference-based indices from DEMQOL and DEMQOL-PROXY for use in economic evaluation. *Health Technol Assess,* 17**,** v-xv, 1-140.

MULHERN, B., SMITH, S. C., ROWEN, D., BRAZIER, J. E., KNAPP, M., LAMPING, D. L., LOFTUS, V., YOUNG, T. A., HOWARD, R. J. & BANERJEE, S. 2012. Improving the measurement of QALYs in dementia: developing patient- and carer-reported health state classification systems using Rasch analysis. *Value Health,* 15**,** 323-33.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (NICE). 2006. *Dementia: Supporting people with dementia and their carers in health and social care* [Online]. http://publications.nice.org.uk/dementia-cg42. . [Accessed 16th June 2014].

RABINS, P. V., BLACKER, D., ROVNER, B. W., RUMMANS, T., SCHNEIDER, L. S., TARIOT, P. N., BLASS, D. M., MCINTYRE, J. S., CHARLES, S. C., ANZIA, D. J., COOK, I. A., FINNERTY, M. T., JOHNSON, B. R., NININGER, J. E., SCHNEIDMAN, B., SUMMERGRAD, P., WOODS, S. M., BERGER, J., CROSS, C.

D., BRANDT, H. A., MARGOLIS, P. M., SHEMO, J. P., BLINDER, B. J., DUNCAN, D. L., BARNOVITZ, M. A., CARINO, A. J., FREYBERG, Z. Z., GRAY, S. H., TONNU, T., KUNKLE, R., ALBERT, A. B., CRAIG, T. J., REGIER, D. A. & FOCHTMANN, L. J. 2007. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry,* 164**,** 5-56.

REISBERG, B. 1984. Functional Assessment Staging (FAST). *Psychopharmacology Bulletin,* 1988**,** 653-659.

RUSSELL, D., HOARE, Z. S., WHITAKER, R., WHITAKER, C. J. & RUSSELL, I. T. 2011. Generalized method for adaptive randomization in clinical trials. *Stat Med,* 30**,** 922-34.

SCHNEIDER, L. S., DAGERMAN, K. S. & INSEL, P. 2005. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA,* 294**,** 1934-43.

SCHNEIDER, L. S., TARIOT, P. N., DAGERMAN, K. S., DAVIS, S. M., HSIAO, J. K., ISMAIL, M. S., LEBOWITZ, B. D., LYKETSOS, C. G., RYAN, J. M., STROUP, T. S., SULTZER, D. L., WEINTRAUB, D. & LIEBERMAN, J. A. 2006. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med,* 355**,** 1525-38.

SMITH, S. C., LAMPING, D. L., BANERJEE, S., HARWOOD, R., FOLEY, B., SMITH, P., COOK, J. C., MURRAY, J., PRINCE, M., LEVIN, E., MANN, A. & KNAPP, M. 2005. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess,* 9**,** 1-93, iii-iv.

SMITH, S. C., LAMPING, D. L., BANERJEE, S., HARWOOD, R. H., FOLEY, B., SMITH, P., COOK, J. C., MURRAY, J., PRINCE, M., LEVIN, E., MANN, A. & KNAPP, M. 2007. Development of a new measure of health-related quality of life for people with dementia: DEMQOL. *Psychol Med,* 37**,** 737-46.

TERI, L., GIBBONS, L. E., MCCURRY, S. M., LOGSDON, R. G., BUCHNER, D. M., BARLOW, W. E., KUKULL, W. A., LACROIX, A. Z., MCCORMICK, W. & LARSON, E. B. 2003. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. *JAMA,* 290**,** 2015-22.

TERI, L., LOGSDON, R. G. & MCCURRY, S. M. 2008. Exercise interventions for dementia and cognitive impairment: the Seattle Protocols. *J Nutr Health Aging,* 12**,** 391-4.

TERI, L., LOGSDON, R. G., UOMOTO, J. & MCCURRY, S. M. 1997. Behavioral treatment of depression in dementia patients: a controlled clinical trial. *J Gerontol B Psychol Sci Soc Sci,* 52**,** P159-66.

TESTAD, I., CORBETT, A., AARSLAND, D., LEXOW, K. O., FOSSEY, J., WOODS, B. & BALLARD, C. 2014. The value of personalized psychosocial interventions to address behavioral and psychological symptoms in people with dementia living in care home settings: a systematic review. *Int Psychogeriatr,* 26**,** 1083-98.

WHITEHOUSE, P. J. 2000. Harmonization of Dementia Drug Guidelines (United States and Europe): a report of the International Working Group for the Harmonization for Dementia Drug Guidelines. *Alzheimer Dis Assoc Disord,* 14 Suppl 1**,** S119-22.