



## Original article

## Essential oils for agitation in dementia [rELOAD]: A pragmatic, cluster-randomized, placebo-controlled, pilot feasibility trial

Matthew J Leach<sup>a,\*</sup>, Merrian Sangalli<sup>b</sup>, Ian Breakspear<sup>c</sup>, Sandra Walsh<sup>d</sup><sup>a</sup> National Centre for Naturopathic Medicine, Southern Cross University, East Lismore, Australia<sup>b</sup> Calmology, Norwood, Australia<sup>c</sup> Endeavour College of Natural Health, Haymarket, Australia<sup>d</sup> Department of Rural Health, University of South Australia, Whyalla Norrie, Australia

## ARTICLE INFO

## Article history:

Received 3 January 2021

Revised 4 May 2021

Accepted 5 May 2021

Available online 26 May 2021

## Keywords:

Agitation  
Aromatherapy  
Clinical trial  
Dementia  
Quality of life

## ABSTRACT

**Background:** Clinical guidelines recommend non-pharmacological interventions as the first line of treatment for agitation in dementia. One intervention that shows some promise as a treatment for agitation is essential oils. The objective of this study was to provide preliminary evidence of the effectiveness and feasibility of using topically-administered, individualized essential oil preparations for the alleviation of agitation in persons with dementia.

**Methods:** We conducted a 10-week pragmatic, cluster-randomized, placebo-controlled, pilot feasibility trial to compare the effectiveness of topically-administered, individualized essential oil preparations to control (placebo) preparations. Outcomes included frequency and severity of agitation, quality of life, frequency of antipsychotic medication use and physical restraint, incidence of adverse events, and trial feasibility. Participants with dementia and clinically significant agitation were recruited from five residential aged-care facilities across regional South Australia.

**Results:** Thirty-eight participants were randomized from five sites. Accounting for random effects, we found statistically significant differences between the intervention and control groups in Pittsburgh Agitation Scale (PAS) aberrant vocalization sub score, Cohen Mansfield Agitation Inventory (CMAI) verbally agitated sub score and CMAI total score at week 4, but not at weeks 8 (post-intervention) or 10 (follow-up). No significant time-group interactions were observed for other PAS/CMAI scores or sub scores, quality of life - Alzheimer's disease total score, or frequency of physical restraint or as-needed antipsychotic medication. No adverse events were reported in any group.

**Conclusions:** The study findings highlight some promising effects of topically-administered, individualized essential oil preparations for agitation in dementia, and indicate that a large multi-center, cluster-randomized controlled trial of this treatment is feasible.

**Trial registration:** Australian New Zealand Clinical Trial Registry [ACTRN12617001159347].

© 2021 Published by Elsevier B.V. on behalf of Korea Institute of Oriental Medicine.  
This is an open access article under the CC BY-NC-ND license  
(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## 1. Introduction

Dementia is a chronic neurological disorder with escalating global prevalence and burden.<sup>1-3</sup> The behavioral and psychological symptoms of dementia (BPSD) are a constellation of distressing non-cognitive symptoms (e.g. agitation) that frequently accompany dementia.<sup>4,5</sup> Not only can BPSD be distressing to the person liv-

ing with dementia,<sup>5</sup> they can also increase burden of care, cost of care, carer distress, carer depression, and the risk of elder abuse and institutionalisation.<sup>6-9</sup>

One class of medications commonly prescribed for the management of BPSD are antipsychotics.<sup>10</sup> However, there are increasing concerns regarding the high cost and safety of these agents.<sup>11,12</sup> Consequently, most clinical guidelines recommend antipsychotic use only where agitation/psychosis symptoms are severe and there is a high risk of harm to the person with dementia. In all other cases, the first line of treatment should be non-pharmacological interventions.<sup>13-15</sup>

\* Corresponding author at: National Centre for Naturopathic Medicine, Southern Cross University, Military Road, East Lismore, 2480, Australia.  
E-mail address: [matthew.leach@scu.edu.au](mailto:matthew.leach@scu.edu.au) (M.J. Leach).

Aromatherapy is a non-pharmacological intervention that uses plant essential oils (administered via inhalation, ingestion or topical application) for therapeutic purposes. Empirical evidence suggests plant essential oils may assist in the management of agitation and BPSD by acting on the neuro-limbic system, and by up-regulating neurotransmitter synthesis to generate antidepressant, anxiolytic and/or sedative effects.<sup>16,17</sup> Some essential oils also demonstrate anticholinesterase activity *in vitro*<sup>18,19</sup>; a particularly important action in the management of dementia.<sup>20</sup>

Although plant essential oils are a biologically plausible, low-cost and well-tolerated treatment for BPSD, the evidence of effectiveness for BPSD is equivocal.<sup>21</sup> There is also a need to explore the effectiveness of individualized, combination essential oil preparations given that people with BPSD typically manifest a diverse combination of psychopathological features, of which a 'one-size-fits-all' approach is neither appropriate nor patient-centred.<sup>5</sup> In response, this study aims to provide preliminary evidence of the safety and clinical effectiveness of topically-administered, individualized essential oil preparations for the alleviation of agitation in persons with dementia.

## 2. Methods

### 2.1. Design

The Essential Oils for Agitation in Dementia [rELOAD] study was a pragmatic, cluster-randomized, placebo-controlled, pilot feasibility trial. The trial was registered with the Australian New Zealand Clinical Trial Registry [ACTRN12617001159347].

### 2.2. Hypotheses

#### 2.2.1. Primary hypotheses

- Topically-administered, individualized essential oil preparations are effective at reducing (a) frequency of agitation and/or (b) severity of agitation in persons with dementia when compared with control.
- The study is feasible to implement as a larger, longer-term definitive randomized controlled trial.

#### 2.2.2. Secondary hypotheses

- Topically-administered, individualized essential oil preparations are effective at (a) increasing quality of life, (b) reducing frequency of use of PRN (*pro re nata*, or as required) antipsychotic medication, and/or (c) decreasing frequency of physical restraint in persons with dementia when compared with control.
- There is no statistically significant difference in the incidence and severity of adverse events between topically-administered, individualized essential oil preparations and control in persons with dementia.

### 2.3. Settings

Study sites were required to be: (1) a residential aged-care facility located within regional South Australia, (2) a moderate-sized facility with at least 50 beds, and (3) providers of nursing care to persons living with dementia. Participants were recruited from five aged-care facilities located across regional South Australia. Facilities ranged in size from 60 to 100 beds, with each providing high-level care to residents with dementia.

### 2.4. Sample

The study aimed for a sample size of 15 participants per study arm. Based on Browne's flat rule of thumb for two-armed pilot tri-

als,<sup>22</sup> a sample size of 30 participants was considered sufficient for a pilot feasibility trial.

#### 2.4.1. Participant inclusion criteria

Residents were eligible to participate in the study if they met the following criteria: Resident of study site for  $\geq 4$  weeks; diagnosis of dementia (confirmed by Mini-Mental State Examination, DSM-IV criteria or medical diagnosis); evidence of clinically significant agitation (i.e. score of  $\geq 39$  on the Cohen Mansfield Agitation Inventory (CMAI), or score of  $\geq 4$  on the Pittsburgh Agitation Scale [PAS]); and able to provide informed consent directly and/or via substitute decision maker.

#### 2.4.2. Participant exclusion criteria

Residents demonstrating any of the following criteria were ineligible to participate: Concurrent exposure to essential oils in any form, or other novel therapeutic interventions for agitation; history of significant head trauma or brain lesions; or known allergy/sensitivity to any ingredients in the active or control interventions.

### 2.5. Randomisation

Aged-care facilities meeting the site inclusion criteria were randomly assigned (by a researcher not involved in the direct administration of the study) to the intervention or control group, at a ratio of 1:1, using a computer-generated table of random numbers. Randomization codes were held in sequentially-numbered opaque sealed envelopes. Each envelope was selected by a third party (unaware of the allocation sequence) in consecutive order at the time of site enrolment.

### 2.6. Interventions

Participants assigned to the intervention group received 1-2 topical creams (containing a bespoke blend of essential oils [4%] in a cream base, with each product addressing behavioral/emotional symptoms) and 1-2 topical oils (containing a bespoke blend of essential oils [3%] in fractionated coconut oil, with each product addressing behavioral/emotional symptoms). Participants also received (where indicated), a topical ointment (containing a bespoke blend of essential oils [6%] in an ointment base) to address factors suspected of contributing to the patient's agitation. Each formulation was blended by a trained aromatherapist, in accordance with the algorithm presented in Fig. 1.

Participants allocated to the control group received a single control cream (cream base only) and control oil (fractionated coconut oil only). Both groups were topically administered (a) 2.5 mL of each cream 2-4 times daily and PRN and (b) 2.5 mL of each oil 2-4 times daily and PRN, with the intervention group also receiving (c) 1-2 mL of the ointment 2-4 times daily and PRN. The intervention/control was administered for eight weeks. Products and administration times were tailored to the needs of the participant. Staff trained in the administration technique applied (a) each cream to the participant's forearms/face/neck/shoulders (depending on participant preference), (b) each oil to the lower legs, and/or (c) the ointment to the most appropriate site (e.g. site of pain). Fidelity to the intervention/control was assessed using a customized medication administration record.

### 2.7. Blinding

Participants, site staff and the research team were blinded to group assignment. Intervention and control products were provided in identical packaging, and contents matched in color and consistency. To mitigate the risk of potential de-blinding due to

1. Complete patient health history and baseline assessments to ascertain individual needs, preferences, sensitivities and aversions.
2. Exclude all oils from the list of 38 'eligible' (hypoallergenic) oils that are not indicated, contraindicated or disliked by the patient.
3. Select up to five essential oils from the list of remaining eligible oils that best address each of the following: (a) the most frequent and most severe behavioural manifestations of agitation, (b) the most frequent and most severe emotional manifestations of agitation, and/or (c) factors suspected of contributing to the patient's agitation (e.g. pain, insomnia).
4. Adhering to the principles of essential oil blending, add essential oils to a cream base at 4% concentration (creams), a base of fractionated coconut oil at 3% concentration (oils) and/or an ointment base at 6% concentration (ointment).

**Fig. 1.** Algorithm for essential oil selection.

odour, staff and participants were advised that differences in individual formulations would result in variations in product odour, and this should not be misconstrued as an indicator of whether the participant had been assigned the intervention or control.

## 2.8. Outcomes

### 2.8.1. Primary outcomes

Severity of agitation was determined using the 29-item CMAI<sup>23</sup>, and frequency of agitation was measured using the 4-item PAS.<sup>24</sup> Both outcome measures were completed by a senior nurse at baseline (week 0), mid-intervention (week 4), post-intervention (week 8) and follow-up (week 10). Feasibility was determined by measuring recruitment and retention rates, recording participant/staff experiences of the study, and ascertaining fidelity to the intervention. This outcome was assessed on completion of the study.

### 2.8.2. Secondary outcomes

Quality of life (QoL) was measured using the 13-item Quality of Life – Alzheimer's Disease scale (QoL-AD) instrument.<sup>25</sup> Use of PRN antipsychotic medication and use of physical restraint in the two weeks preceding each assessment were recorded on the PAS. These three outcome measures were completed by a senior nurse at weeks 0, 4, 8 and 10. Adverse events were reported by the participant/carer/nursing staff throughout the study using a customised adverse event record, and assessed by the research team at weeks 1, 4 and 8.

## 2.9. Recruitment

Upon completion of a brief seminar describing the trial, nursing staff at each site notified eligible residents and the resident's family about the study. Flyers were also posted throughout study sites, and distributed to eligible residents/substitute decision makers. Study information sessions were also held for substitute decision makers.

Residents/substitute decision makers interested in the study were provided a copy of the participant information sheet. If the resident/substitute decision maker verbalized their intention to consent to participate, the research team arranged for the resident and/or the resident's substitute decision maker to provide written consent.

## 2.10. Procedures

Upon receipt of the signed consent form, the research team completed the participant enrolment form and baseline assessments. Trial advocates (i.e. site staff overseeing the trial) assisted the research team with enrolment documentation and baseline assessments. These assessments were repeated at weeks 4, 8 and 10. Following the baseline assessment, the intervention/control was

commenced, as described above. To monitor adherence/fidelity to the intervention/control, a daily administration record was maintained throughout the intervention period; this was periodically assessed by the trial advocate throughout the trial, and by the research team during scheduled assessments.

## 2.11. Statistical analysis

Data were analyzed by intention-to-treat using SPSS (v.25). A per-protocol analysis was conducted for hypothesis-generating purposes only. Missing data were handled using the multiple imputation method. Means and standard deviations were used to report normally distributed descriptive data, and medians and the interquartile range were used to describe non-normally distributed data. Frequency distributions and percentages were used to describe categorical data. Baseline differences between groups were examined using independent samples t-tests and independent samples median tests for continuous variables, and the Fisher's exact test for categorical variables. Linear mixed-effects models were used to estimate the intervention effect for CMAI, PAS and QoL-AD. The model used restricted maximum likelihood estimation, and included two random effects (i.e. site and participant ID) to account for clustering. Fixed effects included group, time, and time-group interaction. Outcomes were log-transformed as required to improve normality and/or reduce heteroscedasticity.

## 3. Results

Forty-one residents from 5 aged-care facilities were screened (Fig. 2). Three residents were ineligible as they failed to reach the criteria for 'clinically significant agitation'. The remaining 38 residents were randomly assigned to intervention (3 sites, n = 21 participants) and control (2 sites, n = 17 participants). The median number of participants per site was 6 (range 4–11) for the intervention sites, and 8.5 (range 8–9) for the control sites.

Participants were predominantly female (68.4%), aged 82.13 ± 8.09 years, normal weight (mean body mass index 24.26 kg/m<sup>2</sup>), and living with dementia of the Alzheimer's type (44.7%) (Table 1). Frequency of agitation (median CMAI total score, 64 [IQR 58.8,71]), severity of agitation (median PAS total score, 8 [IQR 7,11.8]) and quality of life (median QoL-AD total score, 24 [IQR 20,27.5]) at baseline were largely in the low to mid-range. There were no statistically significant differences between groups at baseline for any demographic variable or outcome measure.

### 3.1. Severity of agitation

Significant improvements in PAS total score and PAS subscores (excluding PAS aggressiveness subscore) were evident in all participants over time, according to the linear mixed model (Table 2). A significant group effect was only observed for changes in PAS

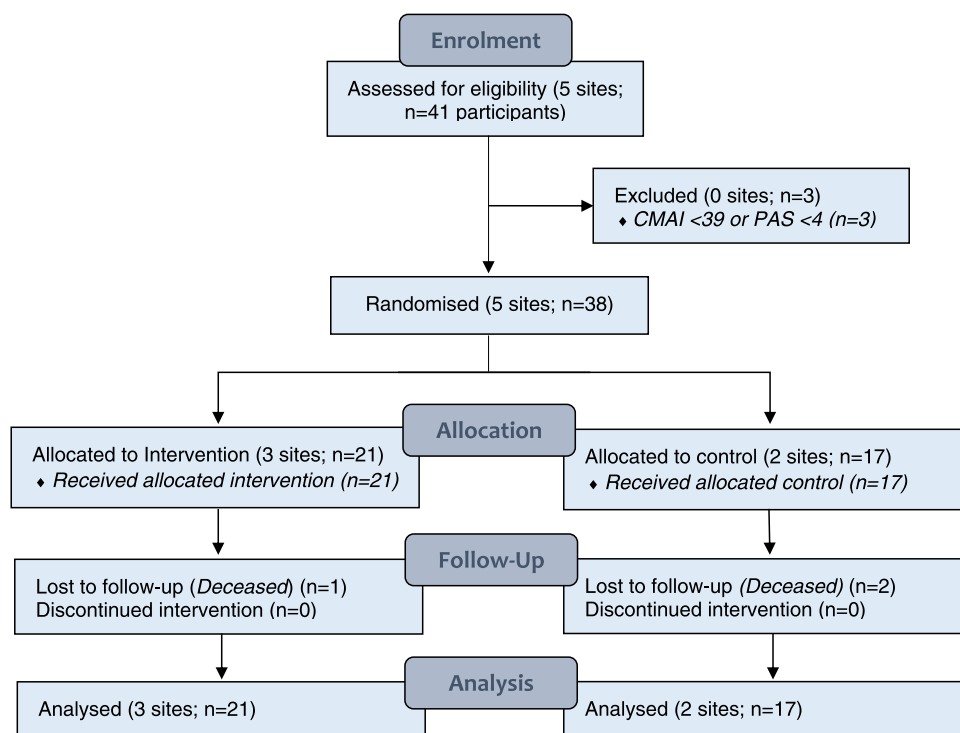


Fig. 2. Participant flow chart.

Table 1  
Baseline characteristics of sample (n = 38)

Characteristic	Intervention group (n = 21)	Control group (n = 17)	p value*
Age, mean (SD)	81.71 ± 7.44	82.65 ± 9.02	0.729
Sex, n (%)			0.161
Female	12 (57.14)	14 (82.35)	
Male	9 (42.86)	3 (17.65)	
Dementia type, n (%)			0.141
Alzheimer's disease	13 (61.91)	4 (23.53)	
Not specified	6 (28.57)	8 (47.06)	
Mixed type	2 (9.52)	3 (17.65)	
Vascular	0 (0.00)	1 (5.88)	
Frontal lobe	0 (0.00)	1 (5.88)	
Restraint authority in place, n (%)			0.532
None	10 (47.62)	10 (58.82)	
Chemical restraint	10 (47.62)	5 (29.41)	
Physical restraint	1 (4.76)	2 (11.77)	
Body mass index [kg/m <sup>2</sup> ], mean (SD)	24.72 ± 4.41	24.14 ± 4.04	0.589
Baseline CMAI total score, median (IQR)	63 (58.5,69.5)	65 (57.5,94)	1.000
Baseline PAS total score, median (IQR)	7 (6,11)	10 (7,14)	0.344
Baseline QoL-AD total score, median (IQR)	24 (21.5,28)	22 (17,28)	0.770

\*means compared using independent samples t-test; medians compared using independent samples median test; categorical data compared using Fisher's Exact test

CMAI, Cohen Manfield Agitation Inventory; IQR, Interquartile range; PAS, Pittsburgh Agitation Scale; QoL-AD, Quality of life in Alzheimer's disease scale.

aberrant vocalization subscore ( $p = 0.018$ ). Accounting for random (subject and clustering) effects, participants in the intervention group demonstrated a statistically significant reduction in PAS aberrant vocalisation subscore (time-group interaction,  $-0.16$ ; 95% CI  $-0.03$  to  $-0.29$ ;  $p = 0.020$ ), and a marginally significant reduction in PAS total score (time-group interaction,  $-0.21$ ; 95% CI  $-0.43$  to  $0.01$ ;  $p = 0.058$ ), at week 4 when compared with control. No significant time-group interactions were observed at weeks 8 and 10. Controlling for the effect of treatment compliance had little impact on these estimates.

### 3.2. Frequency of agitation

The linear mixed model showed significant reductions ( $p \leq 0.001$ ) in CMAI total score and CMAI subscores among

all participants over time (Table 2). While changes in CMAI total score (median change, 22 [33.9%, control] vs. 13 [20.6%, intervention]) and CMAI physically aggressive subscore (median change, 5 [31.3%, control] vs. 2 [12.5%, intervention]) were relatively larger in the control group than the intervention group over time, group assignment and time-group interaction had no significant effect on scores (Table 2). For CMAI verbally agitated subscores, there was a statistically significant group effect ( $p = 0.012$ ) and time-group interaction effect ( $p = 0.024$ ). Accounting for random effects, participants in the intervention group demonstrated a significant reduction in CMAI verbally agitated subscores (time-group interaction,  $-5.10$ ; 95% CI  $-1.44$  to  $-8.76$ ;  $p = 0.007$ ) and CMAI total scores (time-group interaction,  $-8.19$ ; 95% CI  $-0.45$  to  $-15.9$ ;  $p = 0.039$ ) at 4 weeks when compared with control. No significant time-group interactions were observed at weeks 8 and 10. There was little

**Table 2**  
Pittsburgh Agitation Scale (PAS), Cohen Manfield Agitation Inventory (CMAI), and Quality of life – Alzheimer's disease (QoL-AD) scores over time, by group

Measurement	Intervention group (n = 21)	Control group (n = 17)	p value*	Mixed model analysis with interactions	
				Fixed effect	p value#
<b>PAS - total score, median (IQR)</b>					
Week 0	7 (6,11)	10 (7,14)	0.344	Time	<0.001
Week 4	4 (3,7)	6 (4,9)	0.770	Group	0.857
Week 8	5 (4,8)	3 (2,10)	0.945	Time^Group	0.018
Week 10	6 (3,9)	5 (2,8)	0.514		
<b>PAS – aberrant vocalisation subscore, median (IQR)</b>					
Week 0	2 (1,3)	4 (3,4)	0.001	Time	<0.001
Week 4	1 (0,2)	2 (1,3)	0.050	Group	0.018
Week 8	0 (2,1)	1 (3,1)	0.770	Time^Group	0.004
Week 10	1 (0,2)	1 (0,2)	0.821		
<b>PAS – motor agitation subscore, median (IQR)</b>					
Week 0	2 (1,3)	3 (2,4)	0.133	Time	<0.001
Week 4	1 (1,2)	1 (0,3)	0.945	Group	0.745
Week 8	2 (0,2)	1 (0,2)	0.468	Time^Group	0.130
Week 10	2 (1,3)	1 (0,3)	0.926		
<b>PAS – aggressiveness subscore, median (IQR)</b>					
Week 0	2 (0,2)	2 (1,4)	0.427	Time	0.053
Week 4	0 (0,2)	1 (0,2)	1.000	Group	0.881
Week 8	1 (0,2)	0 (0,2)	0.310	Time^Group	0.343
Week 10	1 (0,4)	0 (0,2)	0.310		
<b>PAS – resisting care subscore, median (IQR)</b>					
Week 0	2 (2,3)	3 (2,3)	0.950	Time	<0.001
Week 4	2 (0,2)	1 (0,3)	0.677	Group	0.881
Week 8	2 (1,3)	0 (0,3)	0.926	Time^Group	0.699
Week 10	2 (1,2)	2 (0,3)	0.984		
<b>CMAI - total score, median (IQR)</b>					
Week 0	63 (59,69)	65 (59,92)	1.000	Time	<0.001
Week 4	46 (42,47)	47 (38,71)	0.375	Group	0.340
Week 8	51 (46,55)	41 (37,75)	0.192	Time^Group	0.070
Week 10	50 (37,55)	43 (34,70)	0.514		
<b>CMAI – physically aggressive subscore, median (IQR)</b>					
Week 0	16 (12,24)	16 (13,22)	0.945	Time	0.001
Week 4	15 (13,17)	11 (11,17)	0.192	Group	0.964
Week 8	14 (12,19)	11 (11,14)	0.273	Time^Group	0.306
Week 10	14 (11,19)	11 (11,14)	0.273		
<b>CMAI – physically non-aggressive subscore, median (IQR)</b>					
Week 0	28 (19,32)	26 (23,32)	0.718	Time	<0.001
Week 4	18 (14,20)	14 (13,30)	0.514	Group	0.891
Week 8	19 (15,25)	16 (13,23)	0.468	Time^Group	0.412
Week 10	17 (14,25)	16 (11,22)	0.770		
<b>CMAI – verbally agitated subscore, median (IQR)</b>					
Week 0	19 (14,24)	25 (21,28)	0.214	Time	<0.001
Week 4	11 (9,16)	22 (12,28)	0.050	Group	0.012
Week 8	13 (9,17)	18 (12,23)	0.770	Time^Group	0.024
Week 10	12 (8,17)	14 (11,27)	0.770		
<b>QoL-AD - total score, median (IQR)</b>					
Week 0	24 (22,27)	22 (17,27)	0.770	Time	0.159
Week 4	25 (23,27)	20 (16,24)	0.140	Group	0.123
Week 8	25 (21,26)	23 (18,28)	0.192	Time^Group	0.020
Week 10	24 (23,27)	25 (18,30)	0.770		

\* Medians compared using independent samples median test.

# p values associated with type III tests of fixed effects using log-transformed data. IQR, Interquartile range.

variation in these estimates after controlling for the effect of treatment compliance.

### 3.3. Quality of life

Greater improvements in median QoL-AD total scores were observed in the control group over time when compared with the intervention (median change, 3 [12%, control] vs. 0 [0%, intervention]; Table 2). The linear mixed model found no significant difference in QoL-AD total scores over time, or by group assignment, but did show a statistically significant time-group interaction effect ( $\beta = 0.020$ ; Table 2). After adjusting for random effects, participants in the intervention group showed a marginally significant improvement in QoL-AD total scores at 4 weeks (time-group interaction, 2.90; 95% CI -0.28 to 6.08;  $p = 0.073$ ), but not at 8 or 10

weeks, when compared with control. There was little variation in these estimates after controlling for the effect of treatment compliance.

### 3.4. Use of PRN antipsychotic medication

Fewer participants in the intervention group required PRN antipsychotic medication in the week preceding the week 0, 4 and 10 assessments when compared with control (Table 3). Less PRN antipsychotic medications were dispensed to participants in the intervention group in the week preceding the week 0, 8 and 10 assessments relative to control. However, after accounting for random effects, there was no significant time-group interaction at any time point.

**Table 3**  
Need for PRN antipsychotic medication and physical restraint in the past week, by group and time

Week	Intervention group (n = 21)		Control group (n = 17)	
	Number of participants requiring PRN antipsychotic medication	Number of PRN antipsychotic medications dispensed	Number of participants requiring PRN antipsychotic medication	Number of PRN antipsychotic medications dispensed
Week 0	3 (14.3%)	6	6 (35.3%)	15
Week 4	3 (14.3%)	8	5 (29.4%)	5
Week 8	5 (23.8%)	14	5 (29.4%)	18
Week 10	3 (14.3%)	6	4 (23.5%)	20
	<b>Number of participants requiring physical restraint</b>	<b>Number of times physical restraint was required</b>	<b>Number of participants requiring physical restraint</b>	<b>Number of times physical restraint was required</b>
Week 0	0 (0.0%)	0	1 (5.9%)	7
Week 4	0 (0.0%)	0	5 (29.4%)	11
Week 8	0 (0.0%)	0	4 (23.5%)	10
Week 10	1 (4.8%)	7	2 (11.8%)	2

PRN, as needed.

### 3.5. Use of physical restraint

The number of participants requiring physical restraint in the week preceding each assessment was lower in the intervention group relative to control, at all time points (Table 3). Participants in the intervention group also required physical restraint less often than those in the control group, at each time point. Adjusting for random effects showed no significant time-group interaction at any time point.

### 3.6. Adverse events

No adverse events were reported by participants in any group, at any time point.

### 3.7. Feasibility

#### 3.7.1. Participant recruitment and retention

There were no difficulties in recruiting the required number of eligible participants for the study. Participant retention was high (92%), with only 3 participants lost to follow-up for reasons unrelated to the intervention (i.e. death).

#### 3.7.2. Participant/staff experience

Staff feedback about the trial and the intervention/control was generally positive. Staff found completing the outcome measures to be helpful in understanding and articulating participant behaviors, and no staff expressed concern about the burden of data collection. Staff administering the intervention/control spoke favorably of the products, including the receptivity of participants to intervention/control administration. Two participants each in the control group and intervention group were averse to the applications however, primarily because they did not like physical contact; in these cases, participants continued to be offered the intervention/control throughout the trial, which were only applied after verbal consent had been given by the participant.

#### 3.7.3. Treatment fidelity

The level of fidelity to the treatment (i.e. percentage of expected applications administered) was lower in the intervention group (Median 38%; IQR 22%,58%; Range 9%–85%), than the control group (Median 73%; IQR 46%,79%; Range 5%–96%); this represented a median difference of 35%, which was statistically significant ( $p < 0.001$ ). Several staff provided explanations for the low level of compliance, including complexity of the protocol (particularly the intervention protocol), uncertainty about the trial/intervention, and absent-mindedness.

## 4. Discussion

This is the first known study to provide preliminary evidence of the effectiveness and feasibility of using a combination of topically-administered, individualized essential oil preparations for the alleviation of agitation in persons with dementia. The findings indicate the intervention may be helpful in reducing severity of agitation, frequency of agitation and quality of life, at least in the first four weeks of treatment. There were also non-significant differences between groups in the need for PRN antipsychotic medication and physical restraint. While participant/staff experience of the trial and the intervention/control was generally positive, and there were no adverse events reported against either treatment, there were some challenges with maintaining treatment fidelity. These findings and challenges are the focus of this discussion.

Our findings show some promise for using topical essential oils for the management of agitation; in particular, reducing the severity and frequency of verbal agitation. The greater improvement in verbal agitation symptoms relative to physical agitation symptoms is a novel finding that has not been demonstrated in other aromatherapy trials to date. While the reason for this finding is not entirely clear, it is possible to surmise from what is known about the etiology of vocal behaviors in dementia.

Vocal behaviors in dementia are often triggered by physical, psychological and/or environmental stimuli.<sup>26–28</sup> Given that the frequency and route of exposure to the intervention and control were comparable, it is unlikely that differences in vocalization behaviors between groups were attributed to changes in environmental stimuli. However, it is possible that changes in these behaviors could have related to improvements in pain and stress, with these symptoms shown to be responsive to the effects of essential oils in previous trials.<sup>29,30</sup> Notwithstanding, these outcomes were not measured in the current study and as such, are only hypothetical; but they would be a useful focus for future research examining the effectiveness of aromatherapy for agitation.

The presence of agitation and other behavioral and psychological symptoms of dementia are shown to be associated with diminished quality of life.<sup>31</sup> It is conceivable then that a reduction in agitation would be commensurate with improvements in wellbeing. While study findings revealed an improvement in participant quality of life during the first four weeks of the intervention, the difference between groups was only marginally significant. We speculate that the non-significant difference between groups in quality of life scores may be attributed to dilution of the treatment effect due a potential therapeutic effect of the control. The findings of a meta-synthesis of eleven qualitative studies illustrates this point, which revealed that the quality of life of people with dementia is

predominantly influenced by connectedness.<sup>32</sup> Given the intimate nature of the intervention and control, it is possible that the act of 'touch' helped forge a closer connection between participants and staff, resulting in an improvement in participant quality of life (in both groups). Another possibility is that poor treatment fidelity leads to suboptimal dosing of the intervention, and a reduced treatment effect.<sup>33,34</sup>

The approach to managing dementia-related agitation has changed considerably over the past decade. What was once standard care (i.e. chemical and physical restraint), is now largely considered unacceptable practice and/or a breach of aged-care rights.<sup>35</sup> This means that the prevalence of these practices would have inevitably started at a low base. Indeed, the vast majority of participants in this trial were not administered PRN antipsychotic medication or physical restraint during the study period. This 'basement' effect might explain why between-group differences in these outcomes did not reach statistical significance.<sup>36</sup> It also raises doubts about the suitability of reporting use of PRN antipsychotic medication or physical restraint as proxy measures of agitation in settings where the use of these interventions is now largely discouraged.

Findings from this pilot feasibility study suggest that it would be feasible to conduct a large randomized controlled trial examining the effectiveness of topical essential oil preparations for agitation in dementia. The research team encountered no difficulties attracting or retaining the required number of participants for the study, or collecting data. Further, staff, family and participants were largely receptive to the intervention/control and trial. Notwithstanding, treatment fidelity was found to be lower in the intervention group than the control group.

Increased complexity of the intervention (e.g. greater number of products) relative to the control most likely explains the difference in treatment fidelity between groups given that other factors impacting fidelity (i.e. uncertainty and absent-mindedness) were expected to be similar between groups. Indeed, intervention complexity is shown to be an important moderator of treatment fidelity.<sup>37</sup> Hence, simplification of the treatment protocol is recommended to improve treatment fidelity in future trials using this therapy.

A potential limitation of this study relates to blinding. While strategies were put in place to mitigate the risk of de-blinding, it is possible that differential odours of the intervention and control products may have led some staff to make an assumption about group assignment. However, this is probably unlikely given that all trial advocates believed their facility had been assigned the active intervention. Notwithstanding, it is not known if other staff administering the intervention/control shared the same view. Other limitations of the study, such as treatment fidelity and potential therapeutic effects of the control, have previously been discussed.

The findings of this study allude to some possible benefits of using topically-administered, individualized essential oil preparations for agitation in dementia. The results also suggest a definitive, multi-center, pragmatic, cluster-randomized controlled trial comparing the effectiveness of topical essential oil preparations to control preparations is feasible in this population. However, it is important that any such trial give due consideration to the recommendations outlined in this paper, including those addressing treatment fidelity, triggers of vocalization behavior and potential therapeutic effects of the control.

## Acknowledgements

The authors would like to thank the staff and residents at each site who kindly participated in the trial.

## Author contributions

Conceptualization: ML and MS. Methodology: ML. Formal Analysis: ML. Investigation: ML and SW. Data Curation: ML. Interpretation of findings: ML, IB, SW and MS. Writing – Original Draft: ML. Writing – Review & Editing: ML, IB, SW and MS. Funding Acquisition: ML.

## Conflict of interest

ML, IB and SW declare no conflicts of interest with respect to the research, authorship, and/or publication of this article. MS is Founder of the company that manufactured the intervention and control products.

## Funding

The research was supported by an Endeavour Research Grant. The funder had no role in the study design, data collection, data analysis, decision to publish, or preparation of the manuscript.

## Ethical statement

The study was reviewed and approved by the Human Research Ethics Committee of the University of South Australia (ID. 0000034997).

## Data availability

The data will be made available on reasonable request to the corresponding author.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.imr.2021.100747](https://doi.org/10.1016/j.imr.2021.100747).

## References

- Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and meta-analysis. *Alzheimers Dement*. 2013;9:63–75.
- Australian Institute of Health and Welfare. *Australia's health 2018. Australia's health series no. 16. AUS 221*. Canberra, Australia: Australian Institute of Health and Welfare; 2018.
- Australian Institute of Health & Welfare. *Dementia in Australia. Cat. AGE70*. Canberra, Australia: Australian Institute of Health & Welfare; 2012.
- Selbaek G, Engedal K, Bergh S. The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review. *J Am Med Dir Assoc*. 2013;14:161–169.
- Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. *Front Neurol*. 2012;3:73.
- Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. *Int Psychogeriatr*. 2004;16:295–315.
- Stall NM, Kim SJ, Hardacre KA, Shah PS, Straus SE, Bronskill SE, et al. Association of informal caregiver distress with health outcomes of community-dwelling dementia care recipients: a systematic review. *J Am Geriatr Soc*. 2019;67:609–617.
- Toot S, Swinson T, Devine M, Challis D, Orrell M. Causes of nursing home placement for older people with dementia: a systematic review and meta-analysis. *Int Psychogeriatr*. 2017;29:195–208.
- Herrmann N, Lanctot KL, Sambrook R, Lesnikova N, Hebert R, McCracken P, et al. The contribution of neuropsychiatric symptoms to the cost of dementia care. *Int J Geriatr Psychiatry*. 2006;21:972–976.
- Janus SI, van Manen JG, Jzerman M, Zuidema SU. Psychotropic drug prescriptions in Western European nursing homes. *Int Psychogeriatr*. 2016;28:1775–1790.
- Harrison SL, Kouladjian O'Donnell L, Milte R, Dyer SM, Gnanamanickam ES, Bradley C, et al. Costs of potentially inappropriate medication use in residential aged care facilities. *BMC Geriatr*. 2018;18:9.
- Tampi R, Tampi D, Balachandran S, Srinivasan S. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. *Ther Adv Chronic Dis*. 2016;7:229–245.
- Laver K, Cumming RG, Dyer SM, Agar MR, Anstey KJ, Beattie E, et al. Clinical practice guidelines for dementia in Australia. *Med J Aust*. 2016;204:191–193.

14. Moore A, Patterson C, Lee L, Vedel I, Bergman H. Fourth Canadian Consensus conference on the diagnosis and treatment of dementia: recommendations for family physicians. *Can Fam Physician*. 2014;60:433–438.
15. Royal Australian & New Zealand College of Psychiatrists. *Professional Practice Guideline 10: Antipsychotic Medications as a Treatment of Behavioural and Psychological Symptoms of Dementia*. Melbourne, Australia: Royal Australian & New Zealand College of Psychiatrists; 2016.
16. de Sousa DP, Silva RHN, Silva EFD, Gavioli EC. Essential oils and their constituents: an alternative source for novel antidepressants. *Molecules*. 2017;22 np.
17. Tsang H, Lo S, Chan C, Ho T, Fung K, Chan A, Au D. Neurophysiological and behavioural effects of lavender oil in rats with experimentally induced anxiety. *Flavour Fragrance J*. 2013;28:168–173.
18. Farag MA, Ezzat SM, Salama MM, Tadros MG, Serya RA. Anti-acetylcholinesterase activity of essential oils and their major constituents from four *Ocimum* species. *Z Naturforsch C*. 2016;71:393–402.
19. Kiendrebeogo M, Coulibaly A, Nebie R, Zeba B, Lamien C, Lamien-Meda A, et al. Antiacetylcholinesterase and antioxidant activity of essential oils from six medicinal plants from Burkina Faso. *Revista Brasileira de Farmacognosia*. 2011;21:63–69.
20. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci*. 2008;63:764–772.
21. Forrester LT, Maayan N, Orrell M, Spector AE, Buchan LD, Soares-Weiser K. Aromatherapy for dementia. *Cochrane Database Syst Rev*. 2014 np.
22. Browne RH. On the use of a pilot sample for sample size determination. *Stat Med*. 1995;14:1933–1940.
23. Finkel SI, Lyons JS, Anderson RL. Reliability and validity of the Cohen-Mansfield Agitation Inventory in institutionalized elderly. *Int J Geriatr Psychiatr*. 1992;7:487–490.
24. Rosen J, Burgio L, Kollar M, Cain M, Allison M, Fogleman M, Zubenko MM. The Pittsburgh agitation scale: a user-friendly instrument for rating agitation in dementia patients. *Am J Geriatr Psychiatr*. 1994;2:52–59.
25. Kasper JD, Black BS, Shore AD, Rabins PV. Evaluation of the validity and reliability of the Alzheimer disease-related quality of life assessment instrument. *Alzheimer Dis Assoc Disord*. 2009;23:275–284.
26. Magri C, Ferry P, Abela S. A review of the aetiology and management of vocal behaviour in dementia. *Malta Medical Journal*. 2007;19:30–35.
27. Wyles C. *Characteristics of vocally disruptive behaviour in residents with dementia in specialist dementia care hospitals and possible interventions*. New Zealand: University of Otago; 2011.
28. Yusupov A, Galvin JE. Vocalization in dementia: a case report and review of the literature. *Case Rep Neurol*. 2014;6:126–133.
29. Lakhan SE, Sheaffer H, Tepper D. The effectiveness of aromatherapy in reducing pain: a systematic review and meta-analysis. *Pain Res Treat*. 2016;2016.
30. Mirzaei F, Keshtgar S, Kaviani M, Rajaeifard A. The effect of lavender essence smelling during labor on cortisol and serotonin plasma levels and anxiety reduction in nulliparous women. *Journal o Kerman Univ Med Sci*. 2009;16:245–254.
31. Appelhof B, Bakker C, Van Duinen-van den Ijssel JCL, Zwijsen SA, Smalbrugge M, Verhey FRJ, et al. The determinants of quality of life of nursing home residents with young-onset dementia and the differences between dementia subtypes. *Dement Geriatr Cogn Disord*. 2017;43:320–329.
32. O'Rourke HM, Duggleby W, Fraser KD, Jerke L. Factors that affect quality of life from the perspective of people with dementia: a metasynthesis. *J Am Geriatr Soc*. 2015;63:24–38.
33. Siemer L, Brusse-Keizer MG, Postel MG, Ben Allouch S, Patrinoopoulos Bougioukas A, Sanderman R, et al. Blended smoking cessation treatment: exploring measurement, levels, and predictors of adherence. *J Med Internet Res*. 2018;20:e246.
34. McFadden T. *Fidelity of implementation*. Ontario, Canada: Ontario Centre of Excellence for Child and Youth Mental Health; 2013.
35. Commonwealth of Australia. *Quality of Care Amendment (Minimising the Use of Restraints) Principles 2019*. Canberra, Australia: Commonwealth of Australia; 2019.
36. Spriensma A, Eekhout I, de Boer M, Luime J, de Jong P, Bahcecitapar M, et al. Analysing outcome variables with floor effects due to censoring: a simulation study with longitudinal trial data. *Epidemiol Biostat Public Health*. 2018;15:1–9.
37. Etchells E, Woodcock T. Value of small sample sizes in rapid-cycle quality improvement projects 2: assessing fidelity of implementation for improvement interventions. *BMJ Qual Saf*. 2018;27:61–65.