Aromatherapy as a Safe and Effective Treatment for the Management of Agitation in Severe Dementia: The Results of a Double Blind, Placebo Controlled Trial

Running Title: Aromatherapy for Agitation in Dementia

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Abstract

Background: Behavioural and Psychological Symptoms in Dementia (BPSD) are frequent and a major management problem, especially for patients with severe cognitive impairment. Preliminary reports have indicated positive effects of aromatherapy using select essential oils, but there are no adequately powered placebo controlled trials . We conducted a placebo controlled trial to determine the value of aromatherapy with essential oil (melissa) for agitation in people with severe dementia.

Method: Seventy two people with clinically significant agitation in the context of severe dementia, residing in NHS care facilities, were randomized to aromatherapy with Melissa (lemon balm) essential oil or placebo (sunflower oil). Changes in clinically significant agitation (Cohen-Mansfield Agitation Inventory -CMAI) and quality of life indices (% social withdrawal and % constructive activities measured with Dementia Care Mapping) were compared between the 2 groups over a 4 week period of treatment.

Results: Seventy-one patients completed the trial. No significant side effects were observed. Sixty percent of the active treatment group and 14% of the placebo treated group experienced a 30% reduction of CMAI score, with an overall improvement in agitation of 35% in patients receiving melissa essential oil and 11% in those treated with placebo (Mann-Whitney U test –MWU - $Z=4.1$, $p<0.0001$). Quality of life indices also improved significantly more in people receiving essential balm oil (% social withdrawal MWU $Z=2.6$ $p=0.005$, %constructive activities MWU Z 3.5 $p=0.001$).

Conclusion: Aromatherapy with essential balm oil is a safe treatment which appears to be efficacious for the treatment of clinically significant agitation in people with severe dementia, with additional benefits for key quality of life parameters.

Key words: Aromatherapy Agitation Dementia Quality of life

Word Count: 2,683

Introduction

Dementia is increasingly an important management problem as the elderly population expands. Although attention is usually focused upon cognitive deficits, more than 50% of people with dementia experience behavioural or psychiatric symptoms, by convention referred to as Behavioural and Psychological Symptoms (BPSD)[1]. They are distressing for the patients[2] and problematic for their carers[3]. Pharmacological treatment with neuroleptic agents is often the first line treatment for these symptoms. There are no trials specifically in people with severe dementia, although moderate efficacy has been demonstrated for the treatment of BPSD with neuroleptic agents from placebo controlled trials in people with mild/moderate dementia (20% above placebo), but in the context of high placebo response rates (40%)[4,5]. Neuroleptics can be poorly tolerated by people with dementia, particularly amongst those with severe dementia, and there is a high risk of adverse events (eg parkinsonism, drowsiness, falls, accelerated cognitive decline[6], increased mortality) and a detrimental impact upon key indicators of quality of life[7], including activities, wellbeing and social interaction.

As a consequence of the potentially harmful side effects of these agents, in the UK the Chief Medical Officer has recommended particular caution when prescribing neuroleptics to people with dementia[8]. In the US legislation has been introduced to regulate the prescription of neuroleptics to nursing home patients[9]. In addition, the Committee for Safety of Medicines has recently expressed specific concerns regarding the potential cardiotoxicity of thioridazine[10], the neuroleptic most widely prescribed for elderly people with dementia.

The most frequent and most persistent BPSD syndrome in patients with severe dementia is agitation, usually characterized by a combination of aggression (verbal

and/or physical), restlessness and abnormal vocalisations in the context of subjective anxiety[11]. Therefore, particularly for those with severe dementia, there is an urgent need to identify safe and well tolerated treatment paradigms for behavioural disturbance, especially for the management of agitation.

Aromatherapy using extracts of select plant species offers one possible alternative. Aromatherapy has been used at least since 3000BC, and knowledge of the distillation of essential oils and their application to improve health and wellbeing was introduced into Europe in the 10th century. There is however a clear need to evaluate efficacy in placebo controlled trials. Although the mechanisms of action have not been investigated scientifically to any extent, it is considered likely, that, amongst other effects, the volatile constituents in the essential oils exert physiological effects as a result of absorption through the skin and /or respiratory system[12].

Several plant species are used in medical herbalism for their effect upon symptoms such as anxiety, restlessness, excitability and depression[13,14]. These include Melissa or lemon balm, lavender, chamomile, valerian and vervain. Melissa has been widely used by medical herbalists for the treatment of excitability, restlessness, anxiety, stress and insomnia[13]; and possesses a profile of bioactivity potentially relevant to dementia therapy, including nicotinic actions[15,16]. In addition, the safety of treatment with balm essential oil has been well established in clinical populations[17].

A series of case reports has indicated some potential benefit[18], supported by the findings of a pilot placebo controlled trial of melissa and lavender in 12 dementia patients, although the small numbers precluded formal statistical analysis[19]. Based upon this promising preliminary evidence and the absence of any other safe established

treatments for BPSD in severe dementia, we undertook a double blind, placebo controlled trial, to evaluate the efficacy of aromatherapy using essential balm oil as a therapeutic strategy for the treatment of clinically significant agitation in people with severe dementia. We hypothesised that melissa aromatherapy would result in a significant improvement in agitation compared to placebo, with consequent benefits in key quality of life parameters.

Method

Sample

The study included 72 participants with clinically significant agitation from 8 NHS nursing homes caring for people with severe dementia. Agitation was defined as a cluster of symptoms including anxiety and irritability, motor restlessness and abnormal vocalization. These symptoms often lead to disturbed behaviours such as pacing, wandering, aggression, shouting and night-time disturbance; and are well characterized in the Cohen-Mansfield Agitation Inventory[20] (CMAI), a validated scale that has excellent internal consistency[11,20]. Potential participants were screened using the CMAI, the neuropsychiatric inventory (NPI[21]) and the clinical dementia rating scale (CDR[22]). To be clinically significant, agitation had to occur on at least a daily basis and cause moderate or severe management problems for the care staff (as defined on the NPI). Patients were enrolled in the study if they had clinically significant agitation and their dementia was confirmed as severe (CDR stage 3). There were no other exclusion criteria. Concurrent medication was allowed without restriction, but any changes in psychotropic prescription over the course of the study were monitored.

Baseline Assessment

A standardized evaluation was completed which included the CMAI, NPI, Barthel Scale[23] and a physical examination. Given the severity of the dementia, it was impractical to undertake a formal evaluation of cognitive function. Additional assessments were completed using Dementia Care Mapping (DCM[24]), a reliable and valid[24] direct, operationalised, observational method based upon the theoretical socio-psychological theory of personhood in dementia[25]. The method quantifies activities using behavioural category codes, which are recorded every 5 minutes over a 6 hour period of observation during one day, measuring key quality of life parameters such as social withdrawal and engagement in constructive activities. Raters within the current study had to achieve Kappa values for inter-rater reliability of greater than +0.8 with each other and with a senior care mapper in a 6 hour practice assessment for DCM measures before the main study evaluations were commenced. All raters had completed an examined, certificated training course to ensure that the operationalized rules were applied consistently.
For all participants, the assessments were repeated at weekly intervals for 4 weeks, by raters blind to treatment assignment. The same rater completed the baseline and follow-up assessments.

Treatment

Melissa Essential oil was obtained from a commercial supplier (Baldwin's, London) that was able to guarantee the authenticity and purity of the source through the original suppliers. Analysis of the terpene constituents based on gas chromatography (GC) established that these were typical of Melissa essential oil. The concentrations of the terpenes were: citronellal (22%); caryophylline (18%); neral (7%); garaniol (7%); geranyl acetate (3%) and citronallal (4%), which remained stable over 4 weeks (confirmed with a repeat GC).

Ten percent (by weight) melissa oil (active) or sunflower oil (placebo) was combined with the base lotion (containing: Prunus dulcis oil, glycerine, stearic acid, cetearyl alcohol, and tocopheryl acetate). The formulation was dispensed in opaque plastic dispensers (30 ml per bottle) which delivered a metered dose of 0.16 -0.17 g lotion, such that 6 doses twice daily provided a total of 200 mg oil. The lotion was applied topically to the face and both arms twice a day by a care assistant. The full application process, which involved gently applying the cream into the skin, took approximately 1-2 minutes to complete. Compliance was ensured by weighing the bottles at weekly intervals.
The facilities were matched in pairs (according to number of residents) and then assigned randomly (using the toss of a coin), to active treatment or placebo. This was essential to maintain blindness to the treatment allocation, as in each facility only one of the aromatherapy substances was used, preventing comparisons between agents by staff. For the same reason staff were not informed of the nature of either the active treatment or placebo oils. Treatment was continued twice daily for a four week period.

Follow-up evaluation

The baseline assessments were repeated after 4 weeks. The change in the total CMAI score was the primary outcome measure. CMAI subscores, the NPI irritability and aberrant motor behavior scores and the quality of life parameters were evaluated as secondary outcome indicators.

Statistical Evaluation

The difference in total CMAI score between the baseline and 4 week assessment were compared between the 2 groups using the Mann-Whitney U test (non-parametric statistics were used as the data were not normally distributed). The same measure was used to compare the NPI agitation score and the target problem score. This has been

used as a standard indicator of good outcome in many trials of BPSD[4], the proportion of people attaining a 30% improvement in agitation is described. As additional comparisons, the change from baseline to 4 week follow-up in the main outcome measures were evaluated separately in the active treatment and placebo treated groups. Given the multiple comparisons, a p value of 0.01 was taken to indicate statistical significance. Mean weekly changes in the CMAI are shown graphically.
All statistics utilized the SPSS[26] computerized package.

Results

Seventy two people were enrolled in the study, 36 of whom received active treatment. The mean age of participants was 78.5 ± 8.1 years (77.2 active, 79.7 placebo), 43 were female (56% active, 64% placebo) and 33 (92%) of people in each group were taking at least one psychotropic agent. The characteristics of the 2 groups, which were similar in the 2 groups other than a trend towards higher baseline CMAI scores in those receiving active treatment, are shown in table 1.

Seventy-one (99%) participants completed the 4 week trial, one participant receiving active treatment died over the course of the study (unrelated to the study treatment). The results were analyzed using the data from the 71 completers. Over the course of the 4 weeks, 3 (8%) of the people receiving placebo and 2 (6%) of the people receiving active treatment were prescribed additional psychotropic medication because of increasing agitation. No patients were discontinued from neuroleptics. One patient receiving active treatment experienced 2 days of diarrhoea, no other side effects were reported.

Changes in Agitation

The participants receiving the active treatment (CMAI 68.3±15.3→45.2±10.4, Wilcoxon test Z=5.0 p<0.0001) and those receiving the placebo (CMAI 60.6±16.6→53.3±17.6, Wilcoxon test: Z=2.7 p=0.005) experienced significant improvements on the CMAI, with a 35% reduction in the active treatment group and an 11% reduction in the placebo group. Comparing the differences between the active and placebo treatment over the 4 weeks of the trial, the total CMAI improved to a significantly greater extent on active treatment than placebo (Table 2). Twenty-one (60%) of the active treatment group, but only 5 (14%) of the placebo group attained a 30% improvement (Chi^2 16.3 p<0.0001), the threshold generally defined as clinically significant in BPSD intervention trials. The weekly changes for the CMAI are illustrated in table 3, indicating the largest improvements with the active treatment in week 1 of therapy, with gains maintained thereafter. Over the 4 weeks, significant improvements were seen in the domains of physical non aggressive agitation (motor restlessness) and verbal non aggression (shouting, screaming), with a trend for improvement in physical aggression (Table 2).

In view of a trend towards higher baseline CMAI scores in the active treatment group, an evaluation was undertaken using a subset of 30 participants from each group, matched for baseline CMAI score (baseline scores 63.6±11.3 v 64.2±15.9). The reductions in CMAI scores in the active treatment group over the 4 weeks of the study remained significantly greater than in the placebo treated participants (Mann Whitney U test z=2.8 p=0.005).

Changes in Quality of Life

There was a significant reduction in the percentage of time spent socially withdrawn and a significant increase in the percentage of time engaged in constructive activities amongst people receiving active treatment (table 2).

Discussion

This is the first double blind placebo controlled study to evaluate the efficacy of aromatherapy for the treatment of BPSD in patients with severe dementia. Aromatherapy with essential balm oil was well tolerated, and resulted in a 35% improvement in agitation, compared to an 11% improvement with placebo treatment; a highly significant difference ($p<0.0001$). Furthermore, a comparison of the number of people attaining a significant (30%) improvement in each group, indicates that the Number Needed to Treat (NNT) is 4.2; a substantial effect size which compares very favorably with previous pharmacological studies of BPSD in dementia focusing upon less impaired patients[4]. Restlessness and shouting were the domains with the greatest improvement. In contrast to previous reports of neuroleptic treatment, which is associated with increased social withdrawal and decreased engagement in activities[6], aromatherapy also significantly improved quality of life indices. This indicates a benefit in overall wellbeing, in addition to the reduction in agitation, and suggests that improvements were not a consequence of increased sedation, which would have reduced participation in activities.

There are some important methodological issues to consider. As in other studies evaluating the treatment of BPSD, people receiving the placebo treatment experienced a significant improvement, although of a far less substantial magnitude than that seen in the active treatment group. This modest placebo effect is possibly explained by the

increased social contact between staff and residents, and other non specific benefits. As most people with severe dementia have lost any meaningful sense of smell[26], a direct placebo effect due to a pleasant smelling fragrance**,** although possible, is considered to be an unlikely explanation for the positive effects of Melissa in this study. It is possible however, that the fragrance may have had some impact upon the care staff, or influenced ratings to some degree on the informant schedules. It is unlikely however that such factors could be responsible an improvement of this size in the active treatment group alone. In addition, randomization was undertaken by facility to avoid staff being able to make a direct comparison by smell between the test and placebo aromatherapy treatments and hence to maintain the blind design. It is clearly impossible to absolutely control for the differences in odor between aromatherapy oils, although in future studies a placebo with a stronger odor should be included. In the first instance however, the priority was to utilize an inert compound to minimize placebo response. It is a potential risk that the raters may have been able to identify which facilities were receiving active treatment. This is less of a problem for the primary outcome measure pertaining to behavioural evaluations, which were conducted by informant interview and did not hence require close proximity to the people with dementia participating in the trial. It is more of a potential difficulty for the raters completing the observational evaluations, although the operationalized nature of the DCM assessments mitigate against marked bias.

As in the current study application of the essential oil was not linked to any period of extended massage or other sensory stimuli, we would hypothesise that the treatment effect was mediated by the constituent essential oil terpenes, which have previously been shown to exert a physiological effect[28,29]. Monoterpenes are the most common

hydrocarbons in plant essential oils, and one of those present in Melissa, citronellal, is concentrated in the hippocampus after administration to experimental animals[30].

Together with the accumulating case series literature, the present findings indicate the need for multi-centre trials. In the current study aromatherapy was used in conjunction to clinically prescribed psychotropic medication and not as an alternative. Testing whether aromatherapy is a viable management strategy in place of psychotropic drugs requires further evaluation.

Conclusion

This is the first placebo controlled trial to evaluate the treatment of agitation in people with severe dementia, indicates that aromatherapy with essential balm oil is safe, well tolerated and efficacious, with additional benefits on key quality of life parameters. These findings clearly indicate the need for multi-centre trials investigating the role of aromatherapy as an adjunct and/or an alternative to psychotropic medication for people with agitation in the context of severe dementia.

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Table 1 Baseline Evaluations

	Active Treatment (N=36)	Placebo (N=36)	Evaluation
Cohen Mansfield Agitation Inventory	Med 65.0 IQR 58.3-83.8	Med 58.0 IQR 48.3-67.5	MWU Z=2.3 P=0.02
Age	77.2 (sd 7.6)	79.6 (sd 8.5)	MWU Z=1.4 P=0.16
Female Gender	20 (56%)	23(64%)	Chi^2 0.5 p=0.47
% Social Withdrawal	Med 5.6 IQR 1.4-24.6	Med 3.7 IQR 0-15.5	MWU Z=0.7 P=0.45
% Engaged in constructive activities	Med 28.2 IQR 15.0-46.7	Med 32.2 IQR 17.7-44.6	MWU Z=0.3 P=0.76

MWU - Mann Whitney U test, Med –Median, IQR – Inter-quartile range, SD – Standard Deviation

Table 2

Impact of Treatment upon Agitation and Quality of Life Indices

	Change in Median		Statistical Evaluation
	Active Treatment (N=35)	Placebo (N=36)	
Change in Cohen Mansfield Agitation Inventory (CMAI - total score)	↓ 22.0	↓6.5	MWU Z=4.1 p<0.0001*
CMAI –Physical Aggression	↓ 6.0	↓ 3.0	MWU Z=2.5 P=0.01*
CMAI –Physical Non-Aggression	↓ 9.0	↓ 2.0	MWU Z=4.2 P<0.0001*
CMAI-Verbal Aggression	↓ 1.0	↓ 1.0	MWU Z=0.4 P=0.71
CMAI –Verbal non-aggression	↓ 4.0	↓ 1.0	MWU Z=3.5 p=0.001*
Change in NPI – Irritability score	↓ 3.0	↓ 0.0	MWU Z=4.1 p<0.0001*
Change in NPI-Aberrant motor behaviour score	↓ 4.0	↓ 0.3 (sd 3.8)	MWU Z=4.1 p<0.0001
Change in % Social Withdrawal	↓ 5.6	↑1.4	MWU Z=2.6 p=0.01*
Change in % Engaged in constructive activities	↑6.2	↓ 9.4	MWU Z=3.5 p=0.001

MWU - Mann Whitney U test, SD –Standard deviation

* Statistically significant

Table 3 Weekly Total Cohen Mansfield Agitation Inventory Scores

(The Primary Outcome Measure)

		Baseline	week 1	week 2	week 3	week 4
Active Treatment	Median	65.0	48.5	43.0	46.0	44.0
	IQR	58.3-83.8	47.0-53.5	40.0-46.0	39.0-56.0	37.0-53.0
Placebo	Median	58.0	56.0	54.5	49.5	50.0
	IQR	48.3-67.5	48.3-62.0	40.3-67.5	41.2-65.3	43.3-63.3

IQR – Inter Quartile Range