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

Clive G. Ballard, M.R.C.Psych., M.D.; John T. O'Brien, M.R.C.Psych., D.M.; Katharina Reichelt, M.Sc.; and Elaine K. Perry, Ph.D.

Background: Behavioral and psychological symptoms in dementia are frequent and are 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 of *Melissa officinalis* (lemon balm) for agitation in people with severe dementia.

Method: Seventy-two people residing in National Health Service (U.K.) care facilities who had clinically significant agitation in the context of severe dementia were randomly assigned to aromatherapy with *Melissa* essential oil (N = 36) or placebo (sunflower oil) (N = 36). The active treatment or placebo oil was combined with a base lotion and applied to patients' faces and arms twice a day by caregiving staff. Changes in clinically significant agitation (Cohen-Mansfield Agitation Inventory [CMAI]) and quality of life indices (percentage of time spent socially withdrawn and percentage of time engaged in constructive activities, measured with Dementia Care Mapping) were compared between the 2 groups over a 4-week period of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 (21/35) of the active treatment group and 14% (5/36) of the placebo-treated group experienced a 30% reduction of CMAI score, with an overall improvement in agitation (mean reduction in CMAI score) of 35% in patients receiving *Melissa* balm essential oil and 11% in those treated with placebo (Mann-Whitney U test; $Z = 4.1$, $p < .0001$). Quality of life indices also improved significantly more in people receiving essential balm oil (Mann-Whitney U test; percentage of time spent socially withdrawn: $Z = 2.6$, $p = .005$; percentage of time engaged in constructive activities: $Z = 3.5$, $p = .001$).

Conclusion: The finding that aromatherapy with essential balm oil is a safe and effective treatment for clinically significant agitation in people with severe dementia, with additional benefits for key quality of life parameters, indicates the need for further controlled trials.

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Corresponding author and reprints: Clive Ballard, M.D., Wolfson Research Centre, Newcastle General Hospital, Westgate Rd., Newcastle upon Tyne, United Kingdom NE4 6BE (e-mail: c.g.ballard@ncl.ac.uk).

Dementia is increasingly an important management problem as the elderly population increases. Although attention is usually focused on cognitive deficits, more than 50% of people with dementia experience behavioral or psychiatric symptoms, by convention referred to as "behavioral and psychological symptoms in dementia" (BPSD).[1] They are distressing for the patients[2] and problematic for their caregivers.[3] Pharmacologic treatment with neuroleptic agents is often the first-line treatment for these symptoms. There are no trials specifically in people with severe dementia, although placebo-controlled trials have demonstrated moderate efficacy for the treatment of BPSD with neuroleptic agents in people with mild/moderate dementia (20% above placebo), but in the context of high placebo response rates (40%).[4,5] Neuroleptics are often very poorly tolerated by people with dementia, particularly those with severe dementia, and there is a high risk of adverse events (e.g., parkinsonism, drowsiness, falls, accelerated cognitive decline,[6] and increased mortality) and a detrimental impact on key indicators of quality of life,[7] including activities, well-being, and social interaction.

As a consequence of the potentially harmful side effects of these agents, in the United Kingdom, the Chief Medical Officer has recommended particular caution when prescribing neuroleptics to people with dementia.[8] In the United States, 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 persistent BPSD syndrome in patients with severe dementia is agitation, usually charac-

terized by a combination of aggression (verbal and/or physical), restlessness, and abnormal vocalizations in the context of subjective anxiety.[11] Therefore, particularly for those with severe dementia, there is an urgent need to identify safer and better tolerated treatment paradigms for behavioral disturbance, especially for the management of agitation.

Aromatherapy using extracts of select plant species offers one possible alternative to pharmacotherapy. Aromatherapy has been used since at least 3000 B.C., and knowledge of the distillation of essential oils and their application to improve health and well-being 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, among other effects, including those of a pleasant odor, the volatile constituents in the essential oils exert physiologic 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 on symptoms such as anxiety, restlessness, excitability, and depression.[13,14] These include *Melissa officinalis* (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] On the basis of 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 hypothesized that *Melissa* aromatherapy would result in a significant improvement in agitation compared with placebo, with consequent benefits in key quality of life parameters.

METHOD

Sample

The study included 72 participants with clinically significant agitation from 8 National Health Service nursing homes caring for people with severe dementia. The study was fully approved by the Local Research Ethics Committee. In view of the level of cognitive impairment, assent was obtained from the next of kin as well as consent from the participants. Agitation was defined as a cluster of symptoms including anxiety and irritability, motor restlessness, and abnormal vocalization. These symptoms often lead to disturbed behaviors such as pacing, wandering, aggression, shouting, and nighttime disturbance and are well characterized in the Cohen-Mansfield Agitation Inventory (CMAI),[20] 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 that included the CMAI, NPI, Barthel Scale,[23] and a physical examination. Given the severity of the patients' 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, operationalized, observational method based on the theoretical sociopsychological theory of personhood in dementia.[25] The method quantifies activities using behavioral category codes, which are recorded every 5 minutes over a 6-hour period of observation during 1 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 interrater 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 were examined and certificated in a 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, England) 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 established that they were typical of *Melissa* essential oil. The concentrations of the terpenes were as follows: citronellal (22%), caryophyllene

Table 1. Baseline Evaluations[a]

Variable	Active Treatment (N = 36)	Placebo (N = 36)	Evaluation Test Result[b]	p
Cohen-Mansfield Agitation Inventory score				
Median	65.0	58.0	Z = 2.3	.02
IQR	58.3–83.8	48.3–67.5		
Age, mean (SD), y	77.2 (7.6)	79.6 (8.5)	Z = 1.4	.16
Female gender, N (%)	20 (56)	23 (64)	χ^2 = 0.5	.47
% of time spent socially withdrawn				
Median	5.6	3.7	Z = 0.7	.45
IQR	1.4–24.6	0–15.5		
% of time engaged in constructive activities				
Median	28.2	32.2	Z = 0.3	.76
IQR	15.0–46.7	17.7–44.6		

[a]Abbreviation: IQR = interquartile range.
[b]Chi-square test used for gender; Mann-Whitney U test used for all other variables.

(18%), neral (7%), geraniol (7%), geranyl acetate (3%), and citronallal (4%). The concentrations remained stable over 4 weeks (confirmed with repeat gas chromatography).

Ten percent (by weight) *Melissa* oil (active treatment) 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) that delivered a metered dose of 0.16 to 0.17 g of lotion. A care assistant applied the lotion topically to the patient's face and both arms twice a day for a total of 6 doses per day, providing a total of 200 mg of oil. The full application process, which involved gently applying the cream into the skin, took approximately 1 to 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. All of the participants residing in a specific facility received the treatment assigned to that particular location. This was essential to maintain blindness to the treatment allocation, as in each facility only 1 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 4-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, NPI irritability and aberrant motor behavior scores, and 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 was compared between the 2 groups using the Mann-Whitney U test (nonparametric statistics were used since the data were not normally distributed). The same measure was used to compare the NPI agitation score. Thirty percent improvement in agitation is the standard indicator of good outcome. The proportion of people attaining this level of improvement in agitation is described. As additional comparisons, the change from baseline to 4-week follow-up in the main outcome measures was evaluated separately in the active treatment and placebo-treated groups. Given the multiple comparisons, a p value of .01 was used to indicate statistical significance.

The SPSS[26] computerized package was used for all statistical analysis.

RESULTS

Seventy-two people were enrolled in the study, 36 of whom received active treatment. The mean ± SD age of participants was 78.5 ± 8.1 years (active treatment, mean = 77.2 years; placebo, mean = 79.6 years), 43 were female (active treatment, 56%; placebo, 64%), and 33 (92%) in each group were taking at least 1 psychotropic agent. The characteristics of the 2 groups were similar except for a trend toward higher baseline CMAI scores in those receiving active treatment, as shown in Table 1. When the characteristics of participants at different sites were compared, there were no significant differences (analysis of variance: age, F = 0.71, p = .82; baseline total CMAI, F = 1.3, p = .25; chi-square: gender, χ^2 = 6.3, df = 7, p = .51).

Seventy-one participants (99%) completed the 4-week trial; 1 participant receiving active treatment died during 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 diarrhea; no other side effects were reported.

Changes in Agitation

The participants receiving the active treatment (CMAI score at baseline, 68.3 ± 15.3; at endpoint, 45.2 ± 10.4; Wilcoxon test Z = 5.0, p < .0001) and those receiving the placebo (CMAI score at baseline, 60.6 ± 16.6; at endpoint, 53.3 ± 17.6; Wilcoxon test Z = 2.7, p = .005) experienced significant improvements on the CMAI, with a 35% reduction in the active treatment group and an 11% reduction in the placebo group. When the differences

Table 2. Impact of Treatment on Agitation and Quality of Life Indices[a]

Measure	Change in Median: Active Treatment (N = 35)	Change in Median: Placebo (N = 36)	Statistic[b]: Z	Statistic[b]: p
CMAI				
Total score	↓ 22.0	↓ 6.5	4.1	< .0001[c]
Physical aggression	↓ 6.0	↓ 3.0	2.5	.01[c]
Physical nonaggression	↓ 9.0	↓ 2.0	4.2	< .0001[c]
Verbal aggression	↓ 1.0	↓ 1.0	0.4	.71
Verbal nonaggression	↓ 4.0	↓ 1.0	3.5	.001[c]
NPI				
Irritability score	↓ 3.0	↓ 0.0	4.1	< .0001[c]
Aberrant motor behavior score	↓ 4.0	↓ 0.3[d]	4.1	< .0001[c]
% of time spent socially withdrawn	↓ 5.6	↑ 1.4	2.6	.005[c]
% of time engaged in constructive activities	↑ 6.2	↓ 9.4	3.5	.001[c]

[a]Abbreviations: CMAI = Cohen-Mansfield Agitation Inventory, NPI = Neuropsychiatric Inventory.
[b]Mann-Whitney U test.
[c]Statistically significant.
[d]Standard deviation = 3.8.

between the active and placebo treatment over the 4 weeks of the trial were compared, total CMAI score improved to a significantly greater extent with active treatment than with placebo (Table 2). Twenty-one subjects (60%) in the active treatment group, but only 5 (14%) in the placebo group, attained a 30% improvement ($\chi^2 = 16.3$, $p < .0001$), 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. During the 4 weeks, significant improvements were seen in the domains of physical nonaggressive agitation (motor restlessness), verbal nonaggression (shouting, screaming), and physical aggression (see Table 2).

An additional linear regression analysis was undertaken using the primary outcome measure (difference from baseline to conclusion of the study in the total CMAI score) as the dependent variable, and the treatment condition and sites as the independent variables. Treatment condition (active vs. placebo) was entered into the equation ($t = 3.5$, $p = .001$), but residing at different sites was excluded (site 1, $t = 0.81$, $p = .43$; site 2, $t = 0.28$, $p = .78$; site 3, $t = 1.6$, $p = .11$; site 4, $t = 0.12$, $p = .90$; site 5, $t = 0.12$, $p = .90$; site 6, $t = 0.79$, $p = .43$; site 7, $t = 1.1$, $p = .29$; site 8, $t = 1.1$, $p = .29$).

In view of a trend toward 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: active treatment, 63.6 ± 11.3 vs. placebo, 64.2 ± 15.9). The reductions in CMAI scores in the active treatment group during the 4 weeks of the study remained significantly greater than in the placebo-treated participants (Mann-Whitney U test $Z = 2.8$, $p = .005$).

Table 3. Weekly Total Cohen-Mansfield Agitation Inventory Scores (primary outcome measure)[a]

Group	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

[a]Abbreviation: IQR = interquartile range.

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 among people receiving active treatment (Table 2).

DISCUSSION

Ours 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 with an 11% improvement with placebo treatment, a highly significant difference ($p < .0001$). Furthermore, a comparison of the number of people attaining a clinically significant (30%) improvement in each group indicates that the number needed to treat is 4.2, a substantial effect size that compares very favorably with previous pharmacologic studies of BPSD in dementia focusing on 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 scores on quality of life indices. This improvement indicates a benefit in overall well-being, 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. Randomization was undertaken on the basis of 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. In addition, 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 and a more systematic evaluation of the awareness of whether the received treatment was an active therapy or a placebo would be beneficial. In this study, 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 behavioral evaluations, which were conducted by informant interview and hence did not require close proximity to the people with dementia participating in the trial. It is more of a potential difficulty for the observational evaluations, which were completed by raters, although the operationalized nature of the DCM assessments mitigates against marked bias.

There are several hypotheses that may explain the treatment effect. Since application of the essential oil was not linked to a period of extended massage or other sensory stimuli, the treatment effect may be mediated by the impact of the pleasant aroma on the patient or staff or by the constituent essential oil terpenes, which have previously been shown to exert a physiologic effect.[27,28] 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.[29] Another possible explanation for the effect is the increased social contact between staff and residents and other nonspecific benefits. As most people with severe dementia have lost any meaningful sense of smell,[30] 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 on the care staff or influenced ratings to some degree on the informant schedules. It is unlikely that such factors could be responsible for an improvement of the magnitude seen in the active treatment group. The most important consideration is the large effect size indicating improvements in both agitation and quality of life, which clearly emphasize the importance of further studies in this area and highlight the potential utility of aromatherapy for agitated patients with severe dementia. There are, however, a number of key considerations for future trials, including the clarification of potential mechanisms.

Taken in conjunction with the accumulating case series literature, the present findings indicate the need for multicenter trials, particularly considering that current pharmacologic management approaches for this vulnerable patient population with severe dementia are not based on evidence from double-blind, placebo-controlled trials, are potentially harmful, and are prescribed off label. In the current study, aromatherapy was used in conjunction with clinically prescribed psychotropic medication and not as an alternative to it. 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. The results indicate that aromatherapy with essential balm oil is safe, well tolerated, and highly efficacious, with additional benefits on key quality of life parameters. These findings clearly indicate the need for longer-term multicenter trials investigating the role and mechanisms of action of aromatherapy as an adjunct and/or an alternative to psychotropic medication for the treatment of agitation in people with severe dementia.

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