

Optimal nonpharmacological management of agitation in Alzheimer's disease: challenges and solutions

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Abstract: Many patients with Alzheimer's disease will develop agitation at later stages of the disease, which constitutes one of the most challenging and distressing aspects of dementia. Recently, nonpharmacological therapies have become increasingly popular and have been proven to be effective in managing the behavioral symptoms (including agitation) that are common in the middle or later stages of dementia. These therapies seem to be a good alternative to pharmacological treatment to avoid unpleasant side effects. We present a systematic review of randomized controlled trials (RCTs) focused on the nonpharmacological management of agitation in Alzheimer's disease (AD) patients aged 65 years and above. Of the 754 studies found, eight met the inclusion criteria. This review suggests that music therapy is optimal for the management of agitation in institutionalized patients with moderately severe and severe AD, particularly when the intervention includes individualized and interactive music. Bright light therapy has little and possibly no clinically significant effects with respect to observational ratings of agitation but decreases caregiver ratings of physical and verbal agitation. Therapeutic touch is effective for reducing physical nonaggressive behaviors but is not superior to simulated therapeutic touch or usual care for reducing physically aggressive and verbally agitated behaviors. *Melissa* oil aromatherapy and behavioral management techniques are not superior to placebo or pharmacological therapies for managing agitation in AD. Further research in clinical trials is required to confirm the effectiveness and long-term effects of nonpharmacological interventions for managing agitation in AD. These types of studies may lead to the development of future intervention protocols to improve the well-being and daily functioning of these patients, thereby avoiding residential care placement.

Keywords: dementia, nonpharmacological, behavioral and psychological symptoms

Introduction

Dementia is one of the most prevalent diseases in older people and constitutes the largest global public health care challenge. According to the 2015 World Alzheimer Report data,¹ nearly 47 million people are living with dementia in 2015, a number that will nearly double every 20 years. Alzheimer's disease (AD) is a specific form of dementia that causes as many as 50%–70% of all dementia cases.² Although cognitive impairment is the central symptom of AD, behavioral and psychological symptoms, such as agitation, often coexist and are a common cause of patient and caregiver distress, institutionalization, and impairment in quality of life.^{3,4} Frequencies of agitation between 13.0% and 50.4% have been

confusion per se".⁸ Although there is no consensus regarding specific behaviors that integrate the concept,⁴ clinicians have identified three subtypes of agitation as follows: physically nonaggressive behavior, aggressive behavior, and verbally agitated behavior.⁹ Interestingly, there appears to be a relationship between agitation and unmet needs originated by a decreased ability to cope with environmental stimulation and to communicate these needs.¹⁰

Pharmacological interventions have been traditionally used in the treatment of agitation, but many studies have documented adverse effects of sedative and antipsychotic drugs, such as worsening cognitive function, higher cerebrovascular side effects, longer hospitalizations, and increased mortality.¹¹ Thus, the use of a nonpharmacological approach as a first-line treatment for agitation in dementia patients has been increasingly recommended.^{12,13} Overall, well-conducted, evidence-based studies on nonpharmacological interventions are lacking. Nonpharmacological approaches address the contextual and/or psychosocial reasons for agitation and avoid the potentially negative side effects of pharmacological treatment. Interventions such as cognitive stimulation/training, behavioral interventions, physical exercise, therapeutic touch, aromatherapy, bright light therapy, music therapy, and multisensory stimulation have shown promising results in decreasing agitation and cognitive impairment in older adults with dementia.^{14,15}

We performed a systematic review of randomized controlled trials (RCTs) focusing on the nonpharmacological management of agitation of AD patients, with the aim of making evidence-based recommendations about the use of specific intervention strategies. Previous systematic reviews on the topic have been published, including studies with dementia patients, but none of these studies analyzed their results according to dementia subtypes.^{12,14–17} Because patients with different subtypes of dementia or different levels of cognitive impairment may present with different levels of agitation and respond differently to interventions, we specifically focused this review on AD patients aged 65 years and above.

This paper had three specific aims as follows: 1) to review the literature on nonpharmacological therapies used to manage agitation in older AD patients over the past 20 years, 2) to assess the specific effectiveness of each nonpharmacological therapy, and 3) to provide evidence-based recommendations about the use of specific therapies and future research on this topic. Exploring these aspects is clinically relevant and has important implications for health service planning.

Methods

Data sources and search strategy

A systematic review of the literature published during the past 20 years (January 1996 to June 2015) was performed. Four computerized electronic databases were searched, including PubMed, Web of Science, PsycINFO, and Scopus, using the following keywords for AD, agitation, and non-pharmacological therapy: randomized controlled trial, Alzheimer*, agitat*, agress*, non-pharmacological, non-drug therap*, acupuncture, aromatherapy, light therap*, massage, touch, music*, group exercise*, activities, snoezelen, multisensory stimulation, social contact*, environmental modification*, caregiver training, behavioral or behavioral management, psychosocial, reminiscence therap*, validation therap*, reality orientation, space retrieval, alternative therap*, intervention*, and staff training.

Two independent reviewers evaluated

(age and sex), study design, level of cognitive impairment, type of intervention, agitation scale, and main findings. A narrative synthesis approach was performed to examine the results. Next, we made recommendations about the clinical use for each nonpharmacological intervention based on the main findings.

Results

The review procedure is described in Figure 1. As shown in the figure, a total of 754 studies were identified; after the removal of duplicates, 476 were considered potentially relevant and were screened for relevant content. From these studies, 402 were excluded on the basis of the title and

abstract, and 74 were retrieved for full-text assessment. In the next phase, 66 were excluded based on the inclusion criteria. Finally, eight studies met the inclusion criteria for the review (Figure 1).

Data synthesis

Studies' characteristics

The characteristics of the studies are listed in Table 1. The eight studies that were included provided data on the effectiveness of music therapy (n=3),¹⁹⁻²¹ bright light therapy (n=2),^{22,23} aromatherapy (n=1),²⁴ therapeutic touch (n=1),²⁵ and psychological interventions with caregivers using behavioral management techniques (BMT) (n=1).²⁶

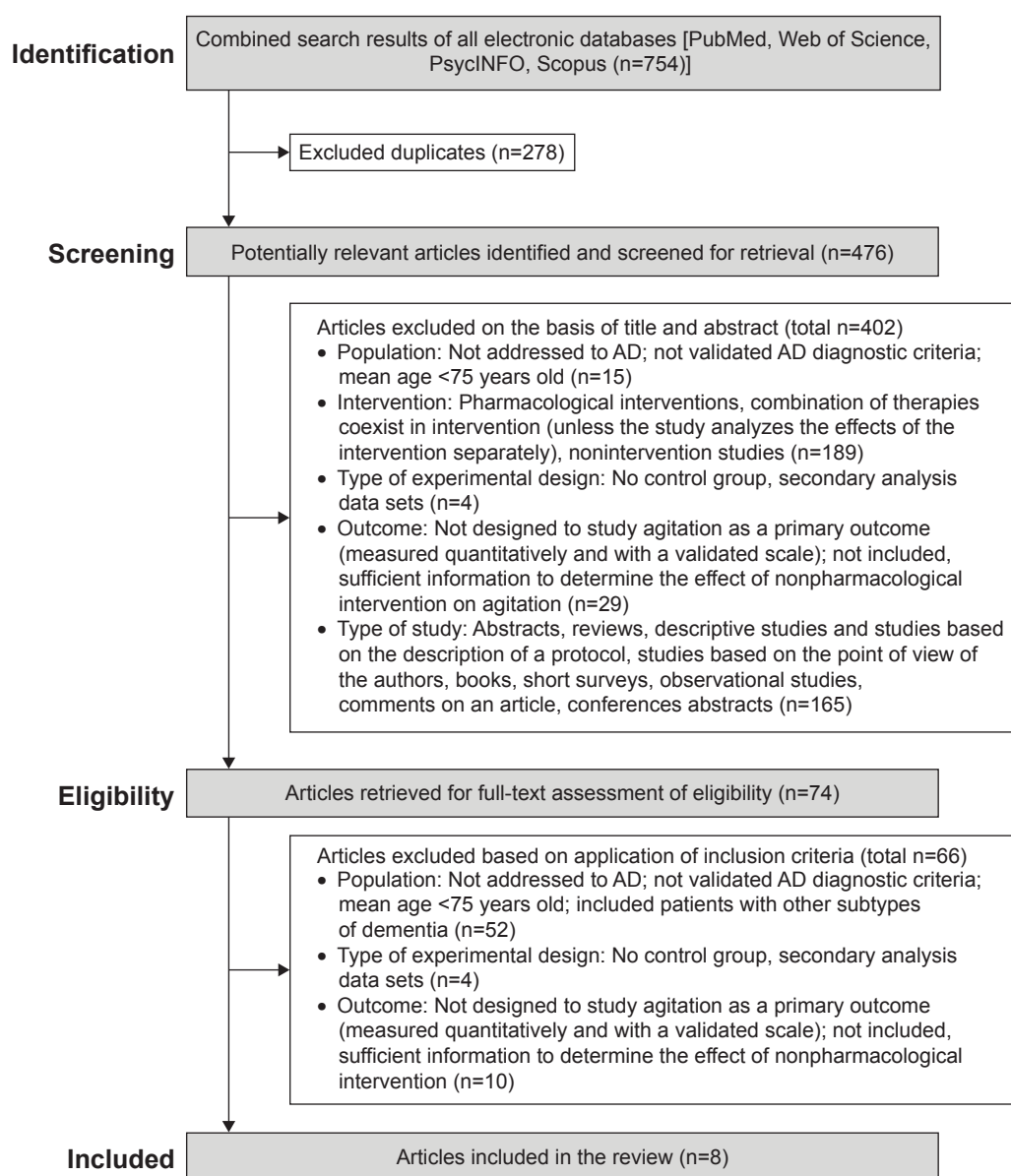


Table 1 Studies included in the review (n=8)

Study	Country	Study design	Level of cognitive impairment	Sample	Therapy	Agitation scale	Main findings
Ancoli-Israel et al ²²	USA	RCT	MMSE = 5.7 ± 5.6	Institutionalized patients with severe AD (n=92; 63 women; mean ± SD = 82.3 ± 7.6, range 61–99) Treatment groups: E1: Morning bright light (n=30) E2: Evening bright light (n=31) C: Control (n=31)	Light therapy N sessions: 10 (1/day, 120 minutes) Duration: 10 days Follow-up: 5 days	CMAI ⁹ ABRS ³¹	CMAI: Caregiver ratings of agitation significantly decreased after treatment in all groups ABRS: No significant effects on observational rating in agitation
Burns et al ²⁴	UK	Multicenter RCT	CDR = 3	Institutionalized AD patients (n=94; 56 women; age range 63–98) Treatment groups: E1: Aromatherapy (Melissa oil; n=32; 21 women, mean age = 85.6) E2: Donepezil (n=31; 21 women; mean age = 84.6) C: Placebo (n=31; 15 women; mean age = 85.1) Institutionalized AD patients (n=70; 57 women; mean age ± SD = 84.0 ± 10.0, range 58–98) Treatment groups: E1: Morning bright light (n=29) E2: Afternoon bright light (n=24) C: Control (n=17)	Aromatherapy N sessions: 2/day (1–2 minutes) Duration: 4 weeks (n=94) Follow-up: week 12 (n=81)	PAS ³² NPI ³⁰	No significant differences between aromatherapy, donepezil, and placebo groups at week 4 and 12 Improvements in all three groups in the PAS and NPI over 12 weeks
Dowling et al ²³	USA	RCT	MMSE = 7.0 ± 7.0	Institutionalized AD patients (n=70; 57 women; mean age ± SD = 84.0 ± 10.0, range 58–98) Treatment groups: E1: Morning bright light (n=29) E2: Afternoon bright light (n=24) C: Control (n=17)	Light therapy N sessions: 1 hour/day (Monday–Friday) Duration: 10 weeks (50 hours)	NPI-NH ³⁰	Significant but possibly potentially not clinically relevant worsening on agitation/aggression after treatment
Hawranik et al ²⁵	Canada	RCT	MMSE = 5.5 ± 6.6	Residents of a long-term care facility with AD (n=51) Treatment groups: E1: Therapeutic Touch (TT; n=17; 10 women; mean age ± SD = 83.3 ± 8.3) E2: Simulated TT (n=16; 14 women; mean age ± SD = 84.2 ± 6.2) C: Usual care (n=18; 12 women; mean age ± SD = 80.9 ± 7.4) Nursing home AD patients (n=37; 32 women) Treatment groups: E: Music (n=18; 15 women; mean age ± SD = 86.			

Svansdottir and Snaedal ²¹	Iceland	Case-control study	GDS = 5-7	Nursing home patients with moderate or severe AD (n=38; age range 71-87) Treatment groups: E: Music therapy (n=20) C: Control (n=18) AD outpatients (n=148) Treatment groups: E1: BMT (n=41; mean age \pm SD = 74.8 \pm 8.4) E2: Haloperidol (n=34; mean age \pm SD = 75.3 \pm 6.9) E3: Trazodone (n=37; mean age \pm SD = 73.2 \pm 6.6) C: Placebo (n=36; mean age \pm SD = 75.8 \pm 6.2) Placebo group: MMSE = 13.0 \pm 8.0	Music therapy N sessions: 18 (30 minutes). 3 times/week Duration: 6 weeks Follow-up: 4 weeks Behavioral Management Training (BMT) N sessions: 11 (8 weekly & 3 biweekly) Duration: 16 weeks	BEHAVE-AD ²⁹	Significant reduction in activity disturbances in the music therapy group
Teri et al ²⁶	USA	Multicenter RCT	BMT group: MMSE = 12.0 \pm 7.0 Haloperidol group: MMSE = 13.0 \pm 8.0 Trazodone group: MMSE = 14.0 \pm 7.0 Placebo group: MMSE = 13.0 \pm 8.0			CMAI ⁹ ABID ³³	No significant differences on agitation across groups. Significantly fewer adverse events in the BMT group

Abbreviations: AD, Alzheimer's disease; ABID, Agitated Behavior Inventory for Dementia; ABRs, Agitated Behavior Rating Scale; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale; BMT, Behavior Management Techniques; C, Control group; CDR, Clinical Dementia Rating Scale; CMAI, Cohen-Mansfield Agitation Inventory; E, Experimental group; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory-Nursing Home; PAS, Pittsburgh Agitation Scale; RCT, Randomized Controlled Trial; N sessions, Number of sessions.

The sample size of the included studies ranged from 37¹⁹ to 148²⁶ AD participants. Three studies were from Europe,^{19,21,24} whereas three studies were from the United States,^{22,23,26} one study was from Asia,²⁰ and one study was from Canada.²⁵ All studies except one²⁶ included institutionalized AD patients in care homes. Two were multicenter studies.<

Inventory for Dementia (ABID).³³ The ABID consists of 16 items designed specifically to evaluate the frequency of common agitated behaviors and caregiver reactions in community-residing dementia patients. Most studies^{19,22,23,25,26} evaluated cognitive status by administering the Mini-Mental State Examination (MMSE).³⁴

Description of the studies

Studies were organized according to the types of nonpharmacological therapy, which are briefly described using Medical Subject Headings (MeSH) definitions.

Music therapy

Music therapy is the use of music as an adjunctive therapy in the treatment of neurological, mental, or behavioral disorders. Three studies^{19–21} provided evidence of the effectiveness of music therapy for reducing agitation in institutionalized patients with moderately severe and severe AD. This result was particularly strong when the intervention included individualized (related to special positive memories of the participants) and interactive (including clapping, singing, and dancing) music.²⁰

One RCT¹⁹ compared the short- and long-term effects of participative music and cooking interventions lasting 4 weeks and reported that both types of pleasant intervention decreased the severity of agitation measured using the CMAI⁹ and NPI.³⁰ The intervention group (n=18) received two 1-hour sessions a week of participatory music therapy (listening to music, singing, and playing percussion instruments), and the control group (n=19) received a cooking intervention (preparing a recipe). Importantly, in the music therapy group, the decrease in agitated behaviors was significant during the intervention (after the fourth session) but not at the end or at the follow-up evaluations (2 and 4 weeks after the intervention). Moreover, this study did not include a no-contact group to ensure that behavioral improvement did not result from increasing familiarity with the supervisor, who had no previous education in music therapy. Because the authors did not take into account individual music preferences, and the supervisor (psychologist) was not a qualified music therapist (and he/she was more comfortable in cooking), the benefit of music therapy observed in this study may have been reduced. Importantly, the improvement in agitation was stronger in the cooking intervention, suggesting that the observed benefits were not specific to musical interventions.

The other RCT²⁰ explored the long-term effects of passive (listening to music via a CD player) or interactive (including clapping, singing, and dancing) music therapy lasting

10 weeks using the BEHAVE-AD²⁹ and reported a higher, long-term reduction in behavioral symptoms in the interactive music group (n=13) compared with the passive music group (n=13) and no-music control group (n=13). Particularly, the scores of five items of the BEHAVE-AD were significantly reduced in the interactive group: paranoid and delusional ideations, activity disturbances, aggressiveness, affective disturbances, and anxieties and phobias; however, this effect disappeared 3 weeks after the music intervention, indicating the need for regularly conducted music interventions to maintain

The other RCT²³ explored the effect of timed morning (n=29) or afternoon bright light (n=24) exposure at 2,500 lux for 1 hour daily compared with usual indoor light levels (n=17; 150–200 lux) in AD patients who experienced rest–activity disruption at baseline. They found a significant but clinically small worsening in agitation/aggression as measured with the NPI-NH³⁰ after 10 weeks of treatment, particularly in the morning-light group. Importantly, the nursing staff was not unaware of the experimental condition of the participants, and the effect of interrater variability on the observed results was impossible to determine in this study.

Aromatherapy

Aromatherapy is the use of fragrances and essences from plants to affect or alter a person's mood or behavior and facilitate physical, mental, and emotional well-being. A multicenter, double-blind, placebo RCT²⁴ explored the effects of aromatherapy with *Melissa officinalis* oil in the treatment of agitation in institutionalized AD patients with a previous history of significant agitation, and found that intervention with *Melissa* oil (n=32) was not superior to placebo (n=31) or pharmacological therapy with donepezil (5 mg/day, n=31) after 4 or 12 weeks of treatment. Agitation was assessed by the PAS³² and NPI.³⁰ The application of *Melissa* oil occurred twice a day and involved massaging the oil into the hands and upper arms for 1–2 minutes. Given the substantial improvement in the placebo group, the authors emphasized the potential benefits of meeting regularly (touch and social interaction) with care staff in the management of agitation in AD patients.

Therapeutic touch

Therapeutic touch is an intentionally directed process during which the practitioner places his or her hands upon the person to be cured with the intent of spiritual energetic healing. One RCT²⁵ compared the effectiveness of therapeutic touch intervention (n=17), which was administered daily for 30–40 minutes for 5 consecutive days, with a simulated therapeutic touch intervention (n=16) and with usual care (n=18) in institutionalized AD patients with a previous history of agitated behaviors. The therapeutic touch intervention was conducted by nurses who had completed the advanced level of a therapeutic touch and healing program, and the simulated therapeutic touch intervention was conducted by nursing and health-related volunteer students. Agitation levels were measured at various times after treatment and then compared. Therapeutic touch was effective in reducing the frequency of physical nonaggressive behaviors (pacing,

repetitious movements, and general restlessness) but was not superior to simulated therapeutic touch or usual care in reducing physically aggressive and verbally agitated behaviors. It is important to note, however, that a significant decrease in the number of all analyzed agitated behaviors was observed in the three groups from baseline to the end of intervention, although this reduction was significantly lower in the usual care group.

Psychological intervention with family caregivers

Psychological therapies imply

in AD,^{19–21} we concluded that music therapy performed by qualified music therapists is an optimal intervention in institutionalized AD patients. The effectiveness of this type of therapy in reducing agitated behaviors has been reported in previous systematic reviews with dementia patients,^{14,15,17,36–38} particularly when based on individual music choices and when complemented by group interventions. Thus, it appears that music therapy is effective for managing agitation in institutionalized dementia patients, potentially because it can engage interest and provides an opportunity for social interaction.

It is important to note that in the three studies, agitated behaviors returned to baseline levels at follow-up, suggesting that music therapy interventions must be implemented on a long-term basis to maintain their beneficial effects. Moreover, the long-term benefits of music therapy remain unclear and require further investigation.

One of the three studies¹⁹ included participants with some previous agitation, whereas the other two studies^{20,21} did not clearly report the previous history of agitation. Thus, the effect of music therapy in AD patients with severe baseline agitation has not been specifically investigated.

Low number and variability among the included studies makes it difficult to identify the most effective duration and frequency of the music intervention. The researchers completed therapy over several weeks (4–10 weeks), with the sessions lasting 30–60 minutes and occurring 1, 2, or 3 times a week; thus, a minimum of 30 minutes of interactive and individualized music therapy twice a week appears reasonable in AD patients. The three trials were small; thus, to strengthen the above evidence, future studies should include larger samples. Finally, it is important to note that the sample was predominantly female, making it difficult to explore differences between the sexes with respect to the effectiveness of music therapy.

Nonpharmacological therapies requiring more research

The inconclusive results of the two studies exploring the effectiveness of bright light therapy^{22,23} and the fact that it may slightly worsen symptomatic agitation indicate that future research is necessary to examine the actual effect of bright light exposure on agitated behaviors in AD patients.

The study by Burns et al²⁴ provided strong evidence indicating that there is no benefit for aromatherapy with *Melissa* oil in the management of agitation in AD, at least over a 12-week period of intervention. Consistent with this finding, a recent systematic review³⁹ of RCTs including dementia patients of any type and severity reported equivocal benefits with aromatherapy.

Regarding the effectiveness of therapeutic touch, the results obtained by Hawranick et al²⁵ provided evidence of the modest potential for this therapy in treating agitated but not physically aggressive behaviors in AD patients with severe cognitive impairment, but additional research is required to obtain evidence about

Given the limited evidence currently available regarding the efficacy of nonpharmacological therapies to manage agitation in AD, there is a strong need for further and more rigorous research. In recent years, multisensory stimulation (MSS) has become a commonly used approach to manage behavioral disturbances and to promote positive mood in dementia patients. MSS actively stimulates the senses of hearing, touch, vision, and smell in an individual-oriented, nonthreatening environment. It is intended to provide individualized, sensory stimulation without the need for higher intellectual activity to achieve or maintain a state of well-being and may be useful in the management of agitation in AD. In previous studies and reviews, it has been demonstrated that MSS produces immediate or short-term positive effects on behavior and mood.^{38,40–46} Future studies are required to assess its effectiveness in this dementia subtype.

Importantly, in the present study, we included only RCTs; it was recently suggested that this likely excludes potent interventions in dementia patients, which limits conclusions.³⁶ Finally, we would like to highlight that although we have made some recommendations providing valuable practical information about the optimal management of agitation in AD patients based on the level of evidence of the reviewed studies, these recommendations are not definitive because clinicians should take into consideration the specific characteristics of their patients or alternative/complementary treatments before using a specific intervention.⁴⁷

Conclusion

This review found that music therapy is an effective nonpharmacological intervention for reducing agitation in institutionalized AD patients, particularly when the intervention implies individualized and interactive music. However, more evidence regarding the long-term effects of this therapy is needed. Bright light therapy has little and potentially no clinically significant effects on agitation levels. Therapeutic touch is effective for reducing physical nonaggressive behaviors but is not superior to simulated therapeutic touch or usual care in reducing physically aggressive and verbally agitated behaviors. *Melissa* aromatherapy and BMT do not appear to be superior to pharmacological therapies or placebo in managing agitation in AD patients; more evidence about their effects on agitation is needed to make definitive clinical recommendations. In general, there is a severe paucity of research into the effects of nonpharmacological therapies in managing agitation in older AD patients.

Author contributions

JCM made the conception of the study and design. CD and BA developed the search strategies, independently screened the title and abstracts of the 754 articles extracted from the literature search, applied the inclusion/exclusion criteria, and retrieved the full electronic text of the eight selected articles. LL and BA extracted the relevant data from the selected articles (independently). LL, BA, and JCM drafted the manuscript. AM and IG provided feedback on the protocol during its development and edited the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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