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A SYSTEMATIC REVIEW OF NONPHARMACOLOGICAL INTERVENTIONS FOR NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE

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ABSTRACT

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All stages of Alzheimer's disease (AD) are characterized by various psychological and behavioral disorders called neuropsychiatric symptoms (NPS). They have a myriad of adverse personal, social, and economic impacts, such as caregiver burden, earlier institutionalization and faster progression of the disease. Prescribing certain psychopharmaceutical drugs to treat the symptoms is common, although they have serious adverse effects. According to formal recommendations, psychosocial interventions are the first choice of treatment for NPS in AD. Little research exists regarding nonpharmacological interventions for NPS in moderate to severe AD, even though the prevalence of this common disease is expected to triple in the near future. To design, target, and implement the nonpharmacological interventions optimally, the complex nature of interventions should be taken into account in research. This systematic review aimed to describe the effects and characteristics of recent nonpharmacological interventions for NPS in moderate to severe AD.

English-language research articles published between January 2009 and November 2020 were searched through the PsycInfo, Medline, and CINAHL databases. In addition, forward and backward reference searches for the included studies and relevant reviews identified through databases were conducted. Randomized and observational study designs were included in the review, and in controlled studies, target interventions had to be compared with other interventions, treatment as usual or "no treatment" condition. The interventions had to be targeted either at participants who had at least a moderate stage of Alzheimer's disease or at their caregivers. In addition, studies were included, if they assessed any NPS in people with Alzheimer's disease (PWA) using validated methods. Articles were first screened by one reviewer and then the final articles were identified by two reviewers based on specific eligibility criteria. One reviewer extracted data and assessed the risk of bias of the study results and the quality of evidence for the primary outcome – in this case, overall NPS at the end of the interventions. Data synthesis for all NPS domains was done by counting the results based on their direction. The interventions were categorized as beneficial, harmful, or inconclusive in relation to any NPS domain used in the study.

Fourteen studies introducing a total of 27 interventions (24 psychosocial, 3 environmental) were included. In one study, the interventions were targeted at caregivers, and the target was PWA in the rest of the studies. Psychosocial interventions for PWA were further classified as stimulation-oriented (60%), behavior-oriented (8%), emotion-oriented (8%), cognition-oriented (4%) and stimulation- and cognition-oriented (4%) interventions. Further, most were recreational therapies in their rehabilitative nature. Out of all interventions, 24 (89%) were classified as beneficial and three (11%) as harmful. Based on the high-quality evidence from RCTs, the nonpharmacological interventions showed significant beneficial effect on overall NPS (12/15, 80%, $p < .05$). The adequate, high-quality evidence showed that stimulation-oriented interventions were beneficial for overall NPS (8/8, 100%, $p < .01$). The very low quality evidence from the observational studies supported the results.

In general, the recreational therapies involving stimulation-oriented activities intended to improve quality of life were beneficial interventions in treating overall NPS in moderate to severe AD. More complex intervention research is needed in different contexts to deepen insight into the subject. When selecting and implementing the intervention in practice, the intervention goals, techniques, and theories should be addressed in relation to the causes for carefully assessed NPS and the characteristics of PWA.

Keywords: Alzheimer's disease, moderate stage, severe stage, neuropsychiatric symptoms, nonpharmacological interventions, complex interventions

TIIVISTELMÄ

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Erilaiset neuropsykiatrisiksi käytösoireiksi kutsutut psyykkiset oireet ja käyttäytymisen häiriöt ovat yleisiä Alzheimerin taudin kaikissa vaiheissa. Niillä on lukuisia haitallisia henkilökohtaisia, sosiaalisia ja taloudellisia seurauksia: ne esimerkiksi lisäävät hoitajien kokemaa kuormitusta sekä nopeuttavat laitoshoitoon joutumista ja sairauden etenemistä. Tiettyjen psyykelääkkeiden määrääminen käytösoireisiin on yleistä, vaikka niillä on vakavia haittavaikutuksia. Virallisten suositusten mukaan psykososiaaliset interventiot ovat Alzheimerin tautiin liittyvien käytösoireiden ensisijainen hoitomuoto. Sairauden keskivaikeaan ja vaikeaan vaiheeseen liittyvien käytösoireiden lääkkeettömistä interventioista on vain vähän tutkimusta, vaikka tämän yleisen sairauden esiintyvyyden odotetaan kolminkertaistuvan lähitulevaisuudessa. Jotta lääkkeettömiä interventioita voitaisiin suunnitella, kohdistaa ja toteuttaa ihanteellisesti, tulisi niiden kompleksisuus huomioida tutkimuksessa. Tässä systemaattisessa katsauksessa kuvailtiin Alzheimerin taudin keskivaikeaan ja vaikeaan vaiheeseen liittyvien käytösoireiden viimeaikaisten lääkkeettömien interventioiden vaikutuksia ja ominaisuuksia.

Tammikuun 2009 ja marraskuun 2020 välisenä aikana julkaistuja englanninkielisiä tutkimusartikkeleita etsittiin PsycInfo, Medline ja CINAHL-tietokantojen kautta. Lisäksi tehtiin eteen- ja taaksepäin suuntautuvat lähdeviitehaut tietokantojen kautta tunnistetuille tutkimuksille ja katsauksille. Katsaukseen sisällytettiin satunnaistettuja ja observationaalisia tutkimuksia. Kontrolloiduissa tutkimuksissa tutkittavaa interventiota piti verrata toisiin interventioihin, tavanomaiseen hoitoon tai "ei hoitoa" -tilanteeseen. Interventioiden tuli olla kohdistettuja joko osallistujille, jotka sairastivat vähintään keskivaikeaa Alzheimerin sairauden vaihetta tai heidän hoitajilleen. Lisäksi Alzheimerin tautia sairastavien henkilöiden (ATH) käytösoireita piti arvioida validoiduin menetelmin. Yhden tutkijan karsimat artikkelit sisällyttiin katsaukseen kelpoisuuskriteerien perusteella kahden tutkijan toimesta. Yksi tutkija keräsi tiedot kyselylomakkeisiin sekä arvioi tutkimustulosten harhan riskin (*risk of bias*) ja ensisijaista tulosmuuttujaa (neuropsykiatriset kokonaiskäytösoireet interventioiden jälkeen) koskevan näytön laadun (*the quality of evidence*). Muutoksia tulosmuuttujissa arvioitiin laskemalla yksittäiset tulokset (*vote counting*) niiden suunnan perusteella. Interventiot luokiteltiin hyödyllisiksi, haitallisiksi tai tuloksettomiksi tutkimuksessa käytetyn tulosmuuttujan muutoksen mukaan.

Katsaukseen sisällytetyt 14 tutkimusta sisälsivät yhteensä 27 interventiota (24 psykososiaalista, 3 ympäristöpsykologista). Yhdessä tutkimuksessa interventiot suunnattiin hoitajille, muissa tutkimuksissa kohteena oli ATH. Psykososiaaliset interventiot ATH:lle luokiteltiin edelleen niiden sisällön mukaan stimulaatiota (60%), käyttäytymistä (8%), emootioita (8%), kognitioita (4%) sekä stimulaatiota ja kognitioita (4%) painottaviksi interventioiksi. Lisäksi suurin osa oli kuntoutukselliselta luonteeltaan virkistysterapeuttisia. Kaikista interventioista 24 (89%) luokiteltiin hyödyllisiksi ja kolme (11%) haitallisiksi. Vahva-asteinen näyttö satunnaistetuista kontrollitutkimuksista osoitti lääkkeettömien interventioiden hyödyn neuropsykiatrisille kokonaiskäytösoireille (12/15, 80%, $p < .05$). Riittävän ja vahva-asteisen näytön mukaan stimulaatiota painottavat interventiot olivat hyödyllisiä kokonaiskäytösoireille (8/8, 100%, $p < .01$). Hyvin heikkoasteinen näyttö observationaalisista tutkimuksista tuki tuloksia.

Stimulaatiopainotteiset, elämänlaadun parantamiseen tähtäävät virkistysterapiat olivat hyödyllisiä interventioita vähintään keskivaikeaan Alzheimerin tautiin liittyvien neuropsykiatristen käytösoireiden hoidossa. Enemmän kompleksista interventiotutkimusta erilaisissa konteksteissa tarvitaan interventioiden kehittämiseksi. Intervention valinnassa ja käytännön toteuttamisessa tulisi suhteuttaa intervention tavoitteita, tekniikoita ja teorioita käytösoireiden syihin ja osallistujien ominaisuuksiin.

Avainsanat: Alzheimerin tauti, keskivaikea vaihe, vaikea vaihe, neuropsykiatriset käytösoireet, lääkkeettömät interventiot, kompleksiset interventiot

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1. INTRODUCTION

Memory diseases constitute an enormous global and public health care challenge that still lacks effective treatments (Nichols et al., 2019). According to the World Health Organization (WHO, 2019), the number of people globally with memory disease probably will rise, mainly due to population growth and aging, from the current 50 million to 152 million by 2050. Memory diseases are associated with the most intense needs for care compared to other conditions; still, a growing number of people with memory disease are cared for at home in low- and middle-income countries where they generally receive little or no help from the health care systems (Prince et al., 2015). The quality of life (QOL) of people with memory diseases is mainly supported by providing help with everyday activities and addressing medical, psychological, and behavioral issues (Prince et al., 2015; Volicer, 2018). However, caregiving is associated with caregiver burden, which, in turn, is related to the neuropsychiatric symptoms (NPS) of the person being treated (Lee et al., 2013).

NPS are highly prevalent in the most common memory disease – Alzheimer's disease (AD; Nowrangi, 2015). These behavioral and psychological symptoms are grouped into five syndromic areas in AD: depression, apathy, sleep, agitation, and psychosis (Geda, et al., 2013). NPS have numerous adverse personal, social, and economic impacts, such as caregiver burden and faster progression of the disease. (Peters et al., 2015). Treatment of NPS should start differentiating which NPS are present and addressing possible contributing causes for them such as comorbidities and unmet needs. Then, nonpharmacological interventions with the strongest evidence base should be tried (Geda et al., 2013; Kales et al., 2014; Lyketsos et al., 2006, Rabins et al., 2017; Volicer, 2018). Yet NPS are seriously undertreated and mistreated (Kales et al., 2014; Lyketsos et al., 2006).

Due to the specific trajectories of decline in social and cognitive domains, people with advanced AD have special needs for care, and their caregivers need more support in managing that care. However, little research exists on effects and characteristics of interventions for people with advanced memory diseases (Rabins et al., 2017; Sampson et al., 2018). The objective of this systematic review is to describe the range, effects, and complexity of recent nonpharmacological interventions for NPS in AD in the moderate to severe stages of AD.

1.1. Alzheimer's disease and related neuropsychiatric symptoms

According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM–5; American Psychiatric Association [APA], 2013), AD is a *major neurocognitive disorder* (NCD). To meet the DSM-5 (APA, 2013) criteria for major NCD due to AD, the criteria should first be met for major NCD by significant cognitive decline from a previous level of cognitive performance, thus interfering with the performance of everyday activities. Second, the criteria encompass the the persistent onslaught and gradually progressive decline in memory and learning at least in one other cognitive domain. Further, the criteria must be met for either *probable* or *possible* AD to be diagnosed. Probable AD is diagnosed if (a) there is evidence of a causative AD-related genetic mutation from family history or genetic testing, or (b) gradual cognitive decline is clearly evidenced by detailed history or serial neuropsychological testing without evidence of mixed etiology. If neither is present, possible AD should be diagnosed.

A number of risk factors contribute to developing AD. Vascular risk factors and vascular morbidity increase the risk of AD, but the strongest risk factor is older age as this contributes to the aging-related biological processes implicated in the pathogenesis of the AD (Qiu et al., 2009). Further, complex interactions between genetic susceptibility and biological, psychosocial, and environmental risk factors accumulate with age. In contrast, protective lifestyle factors strengthen the cognitive reserve and certain physiological and psychological mechanisms (such as relaxation, stress reduction, and positive emotional states), thus supporting cognitive functions in the face of cumulative brain damage (Fratiglioni et al., 2004; Wang et al., 2017).

Among the several specific brain changes associated with AD, the accumulation of the neurofibrillary tangles (NFTs) and senile plaques in the brain are the critical ones (Hyman et al., 2012). Brain changes cause neuronal injury in limbic regions early in the disease and, ultimately, all over the neocortex through predictable pathological stages (Braak et al., 2006; Hyman et al., 2012). These brain changes strengthen the sensitivity to drug effects and predispose to drug-related adverse effects (Pasqualetti et al., 2015). More than half of individuals with AD have brain changes from one or more other memory disease (Alzheimer's Association, 2020). This kind of mixed pathologies is called "mixed dementia" if recognized during life. With the brain changes, the AD continuum has three phases: preclinical AD, mild cognitive impairment (MCI) due to AD, and NCD due to AD (Alzheimer's Association, 2020). The NCD phase is further broken down into the stages of mild, moderate, and severe AD. Eventually, AD leads to death.

AD is characterized by progressive cognitive and functional decline and usually a variety of NPS. The earliest general cognitive deficits in AD are usually the loss of episodic memory and executive function deficits (Aggleton et al., 2016). Gillioz et al. (2009) showed that praxis, orientation, memory, and language were the most impaired domains in people entering the severe stage of AD. However, some forms of memory and general and social cognitions seem to preserve relatively well in AD, including musical memory (Jacobsen et al, 2015), implicit memory, implicit learning systems (Halteren-van Tilborg et al., 2007), and social interaction (Gillioz et al., 2009), among others. Evans-Roberts and Turnbull (2010) demonstrated preserved complex emotion-based learning capacity in moderate AD. Functional impairments in AD refer to the difficulty of performing those basic and complex activities of daily living (ADL) that influence one's capacity to live independently (Sclan & Reisberg, 1992). As for NPS, Table 1 presents the prevalence of and available diagnostic criteria for the five neuropsychiatric syndrome areas in AD proposed by the Neuropsychiatric Syndromes of AD Professional Interest Area (NPS-PIA; Geda et al., 2013).

TABLE 1. Criteria for the neuropsychiatric syndrome areas in Alzheimer's disease (prevalence*)

Depression (42%)

At least three of the symptoms have been present during the same two-week period and at least one of the symptoms must be depressed mood or decreased positive affect / pleasure:

1. Clinically significant depressed mood.
2. Decreased positive affect or pleasure in response to social contacts and usual activities.
3. Social isolation or withdrawal.
4. Disruption in appetite.
5. Disruption in sleep.
6. Psychomotor changes.
7. Irritability.
8. Fatigue or loss of energy.
9. Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt.
10. Thoughts of death, suicidal ideation, plan, or attempt.

Provisional diagnostic criteria; the National Institute of Mental Health (Olin et al., 2002).

Apathy (49%)

A loss of or diminished motivation present. At least one listed symptom in at least two of the three numbered symptom domains has lasted at least four weeks, occurring most of the time:

1. Goal-directed behavior: loss of or diminished self-initiated/environment-stimulated behavior.
2. Goal-directed cognitive activity: loss of or diminished spontaneous/environment-stimulated ideas and curiosity.
3. Emotions: loss of or diminished spontaneous emotions or emotional responsiveness to stimuli or events.

International consensus diagnostic criteria (Robert et al., 2009)

Sleep disturbance due to insomnia (39%)

At least one of the symptoms has lasted at least one month:

1. Difficulties in initiating or maintaining sleep.
2. Poor or non-restorative quality of sleep.

The Neuropsychiatric Syndromes Professional Interest Area of ISTAART (Ancoli-Israel et al., 2013)

Agitation

Specific agitated behaviors are defined by researchers by the items on the rating instruments. The following four dimensions of agitated behaviors have been identified:

1. Physical agitation (32%) versus verbal behaviors.
2. Aggressive (40%) versus nonaggressive behaviors.
3. Directed behaviors versus less purposeful behaviors.
4. Context-dependent behaviors versus generalized behaviors without precipitant.

The Neuropsychiatric Syndromes Professional Interest Area of ISTAART (Sultzer et al., 2013)

Psychosis

At least one of the symptoms has lasted at least one month.

1. Visual and/or auditory hallucinations (16%).
2. Delusions (31%).

The proposed criteria for psychosis in AD (Jeste & Finkel, 2000)

Symptoms should cause significant functional impairments.
* according to Zhao et al. (2016) review

In addition to brain changes and cognitive impairment, interactions between them and the factors related to caregivers, environment, and the person with memory disease explain NPS (Kales et al., 2015). The "caregiver burden" refers to the physical, psychological, emotional, social, and financial strain experienced by caregivers (George & Gwyther, 1986), which is associated with increased depression and anxiety, poorer self-rated health (Schulz et al., 2020), and higher rates of medical illness and mortality (Schulz et al., 2020; Vitaliano et al., 2003) for the caregivers. According to Isik et al. (2019), the caregiver burden triggers and exacerbates NPS in PWA, and vice versa.

According to the Progressively Lowered Stress Threshold model (PLST; Hall & Buckwalter, 1987, as cited in Smith et al., 2004), the behavior of most cognitively impaired persons suggests they suffer from a disordered person-environment interaction. Their dysfunctional behaviors are seen as stress responses to different environmental demands. Cognitively impaired persons' ability to cope with stress deteriorates as the disease progresses, indicating a progressive lowering of the stress threshold. Without intervention, stress-related behavioral patterns seem to follow a certain circadian rhythm: as stressors accumulate throughout the day, anxiety may increase, and the stress threshold may be exceeded, resulting in dysfunctional behaviors later in the day.

As for PWA-related factors explaining NPS, certain biological, clinical, demographic, and psychosocial factors are associated with the frequency and severity of NPS (Robert et al., 2005; Nagata et al., 2017). Biological factors refer primarily to neuropathological, psychopharmacological, and genetic factors (Robert et al., 2005). According to Nagata et al. (2017), the evidence-based demographic factors are age, gender, race, and education, while present cognition levels, ADL-performance, and general medical health – including visual and auditory impairments (Ballard et al., 2020) and pain (Ahn & Horgas, 2013) – are the contributory clinical factors. Further, psychosocial factors describe issues such as premorbid personality, unmet needs, residence type, marital status, life events, and caregiver burden.

The rates of NPS in persons with AD (PWA) vary depending on the assessment methods and diagnostic criteria. The prevalence of NPS in PWA ranged from 80% to 90% in some studies (Steinberg et al., 2004; Tariot et al., 1995; de Vugt et al., 2006, as cited in Nowrangi et al., 2015). Some NPS, like depression, seem to fluctuate and relapse throughout the stages of AD (Geda et al., 2013). However, apathy and depression are common in very early AD (Hallikainen et al., 2012; Lyketsos et al., 2011), and apathy can worsen as the disease progresses (Dillon et al., 2013). Agitation is more prominent in moderate to severe AD (Sultzer et al., 2013), and delusions and hallucinations are more common in advanced than in early stages (Lyketsos et al., 2011).

1.2. Description of the interventions

Nonpharmacological interventions for people with memory diseases have been categorized in more ways than one. Kales et al. (2015) grouped them into interventions that target (a) the person with the disease, (b) their caregivers, and (c) the environment in which PWA lives. In this review, interventions targeting the PWA and the caregivers are referred to as *psychosocial interventions*, while interventions modifying the psychosocial or physical characteristics of the environment associated with everyday life are referred as *environmental interventions*.

Nonpharmacological interventions for PWA have been further divided into mutually overlapping approaches that are (a) behavior-oriented, (b) emotion-oriented, (c) stimulation-oriented, and (d) cognition-oriented (Rabins et al., 2007; Rabins et al., 2017). Behavior-oriented interventions can include, for example, increasing engagement in pleasant activities and maximizing independence (Teri, 1994), as well as training caregivers in the management of problematic behaviors (Rabins et al., 2007). Emotion-oriented interventions can involve psychotherapeutic components such as reminiscence therapy, while stimulation-oriented interventions often consist of recreational activities, art therapies, exercise, multisensory stimulation, simulated presence, and aromatherapy (Rabins et al., 2007). Cognition-oriented interventions are comprised of cognitive stimulation, cognitive training, and cognitive rehabilitation (Rabins et al., 2007; Rabins et al., 2017). Cognitive training focuses on specific cognitive abilities and processes, while cognitive rehabilitation focuses on those cognitive abilities and processes required to perform individually relevant tasks. Cognitive stimulation aims to improve orientation and global cognitive status through general activation and engagement in pleasant activities (Bahar-Fuchs et al., 2020).

Multiple medical organizations and expert groups, such as the American Psychiatric Association practice guideline for treating people with memory disorders (APA; Rabins et al., 2007; Rabins et al., 2017), have recommended nonpharmacological interventions as a first choice of treatment for NPS in AD, except in emergency situations when NPS could compromise safety. In treating overall NPS in AD, the APA guideline recommends behavior-, emotion-, and stimulation-oriented approaches as harmless interventions with moderate confidence (Rabins et al., 2007; Rabins et al., 2017). Cognition-oriented approaches are recommended with less confidence because of the possible frustration they can cause for people with memory diseases. Strong to moderate evidence supports a wide variety of environmental approaches in treating NPS, including person-centered, individually tailored interventions, multisensory interventions, and noise-level regulation, among others (Jensen et al., 2017).

The available research does not systematically show which interventions work best for which settings, specific AD stages, and general patient profile (Rabins et al., 2017). Considering specific stages of AD, the evidence must be collected from reviews addressing AD and memory diseases in general.

Na et al. (2019) conducted a systematic review and meta-analysis focusing on the effects of nonpharmacological interventions on ADL, NPS, cognitions, and QOL of persons with moderate to severe memory diseases. Eleven randomized controlled trials (RCT) met the inclusion criteria, all addressing stimulation-oriented interventions. When compared to the control, beneficial intervention effects on the overall NPS were not found. Yet a positive effect of interventions on depression was found, and one out of these four studies (Rolland et al., 2007) included in the analysis focused solely on AD investigating exercise program in nursing home settings. Subgroup analyses carried out in three studies showed that music therapy was effective in reducing the overall NPS compared to the control. Two out of these three studies focused solely on people with AD. The studies were conducted in a nursing home setting (Narme et al., 2014) and group homes as well as a special dementia hospital (Sakamoto et al., 2013).

Kverno et al. (2009) carried out a systematic review of 21 studies focused on the effects of nonpharmacological interventions on NPS of persons with moderately severe to severe memory diseases. On the whole, they found consistent support for environmental and stimulation-, emotion- and behavior-oriented interventions in treating NPS. Researchers noticed that emotion-oriented interventions may be more effective for individuals with preserved verbal communication skills.

There is no systematic account of which nonpharmacological interventions work best for which individual NPS in AD. Olazarán et al. (2010) found support for individualized exercise programs combined with behavioral management in treating depression in moderate to severe AD (Teri et al., 2003). Furthermore, Guétin et al. (2009) found that music therapy was effective in treating depression and anxiety in mild to moderate AD. Särkämö et al. (2014) showed that both singing and music listening alleviated depression in mild to moderate AD and also in mild stages of other memory diseases (Särkämö et al., 2016). Fukushima et al. (2016) found that six out of eight studies supported cognitive stimulation in treating depression in AD, and two out of two studies supported cognitive stimulation in treating anxiety.

A wide variety of stimulation- and behavioral-oriented interventions have been shown to be effective regarding both apathy (Fukushima et al., 2016; Lanctôt et al., 2017) and agitation in AD (Millán-Calenti et al., 2016; Sultzer et al., 2013; Theleritis et al., 2017; Theleritis et al., 2018). Moreover, environmental interventions are consistently supported in treating agitation and wandering

in AD (Futrell et al., 2014; Jensen & Padilla, 2017). As for sleep in AD, several reviews have shown that sleep is improved by environmental bright light therapy as well as mutually overlapping, psychosocial sleep hygiene, behavioral measures, and psychoeducational behavior programs (Bliwise, 2004; Peter-Derex et al., 2015; Salami et al., 2011; Urrestarazu & Iriarte, 2016). There is scant data focused specifically on treating psychosis in AD using non-pharmacological approaches. Psychosocial and environmental interventions in general are supposed to prevent or delay the onset of psychosis in AD (Sweet et al., 2013).

1.3. How might the interventions work

Engaging people with memory diseases in appropriate activities has been shown to have a wide range of beneficial behavioral effects. The Comprehensive Process Model of Engagement (CPME; Cohen-Mansfield et al., 2009) defines engagement "as the act of being occupied or involved with an external stimulus." Furthermore, the resulting change in affect influences the behavior. The evidence-based model proposes that engagement with a stimulus is affected by interactions between the characteristics of environment (Cohen-Mansfield et al., 2010), person, and stimulus (Cohen-Mansfield et al., 2009). In general, social stimuli, especially one-on-one interaction, are the most engaging stimuli, but exposure to any appropriate stimulus is preferable to no stimulation at all (Cohen-Mansfield et al., 2011).

According to Clements-Cortés (2020), the experiences that the musical interventions offer for PWA range between recreational and therapeutic ones, and they can be more or less receptive or active. The same can be considered to apply to the primary components of most psychosocial nonpharmacological interventions for NPS in AD. Similarities may be found between the rehabilitative nature of interventions; however, leisure facilitation interventions (LFIs), recreational therapies (RTs), and psychotherapies include separate scientific practices having their own traditions, goals, techniques, and theories of mechanisms of action. LFIs do not have the specific health-related therapeutic goals but are aimed at increasing enjoyment through the leisure techniques (Austin et al., 2020). Instead, RTs and psychotherapies represent the health care professions; these have specific health-related therapeutic goals that are pursued by means of a predefined process of implementation and therapeutic relationship. RTs allow clients to engage in evidence-based, enjoyable recreation and leisure activities that help them to self-actualize and to restore, maintain, or enhance their wellness and health (Austin et al., 2020). Psychotherapy employs evidence-based, psychological techniques

and dialogue to identify and change the clients' problematic thought and behavior patterns (American Psychological Association [APA], 2020).

Nonpharmacological interventions for NPS in AD are *complex interventions*: they are comprised of multiple components (intervention complexity) and achieve their results through complex pathways (pathway complexity). Furthermore, they may also involve population, implementation, or contextual complexity (Guise et al., 2017). A logic model makes it possible to graphically describe the system and identify important pathways and relationships between the elements within that system (Anderson et al., 2011). Figure 1 depicts the adapted Comprehensive Process Model of Engagement of Persons With Dementia (Cohen-Mansfield et al., 2009) as a logic model of intervention and pathway complexities of primary interest in this review.

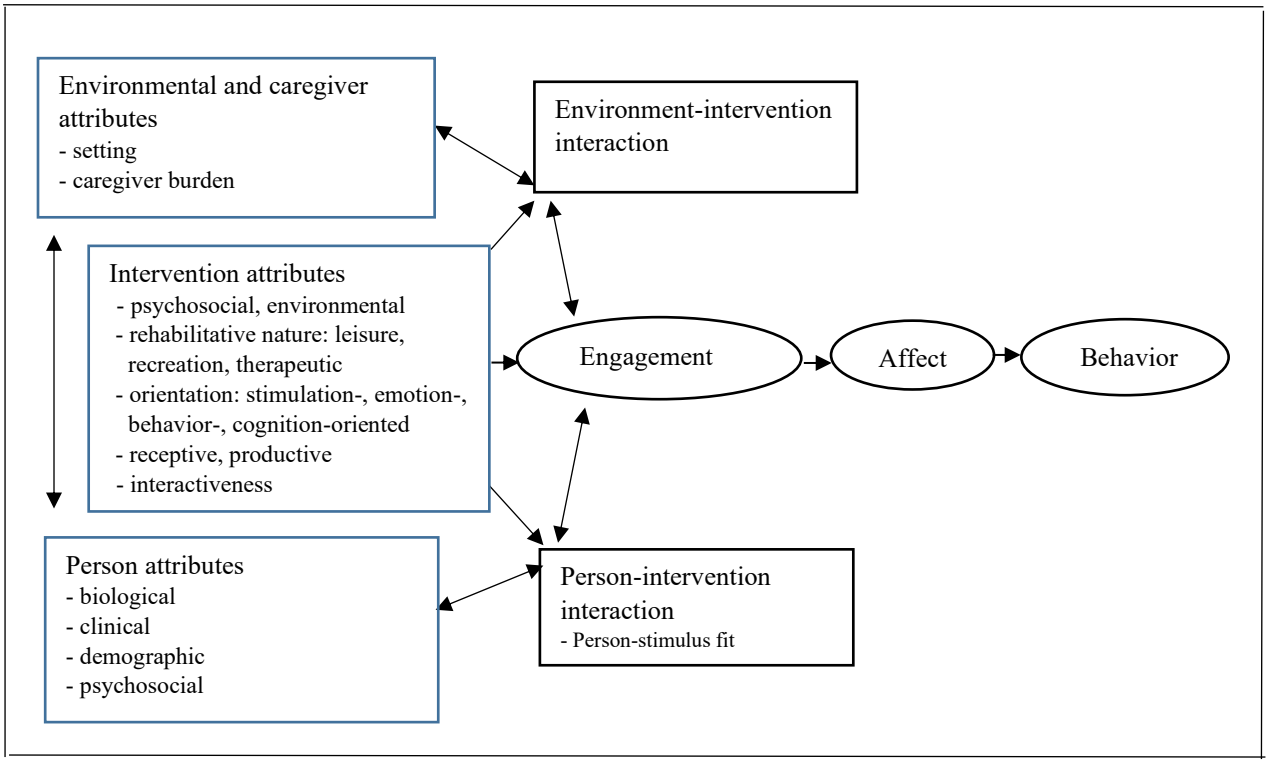

FIGURE 1. The complexity of non-pharmacological interventions captured by the adapted Comprehensive Process Model of Engagement of Persons With Dementia (Cohen-Mansfield et al., 2009).

1.4. Objectives

The purpose of this systematic review is to describe the range and the effects of recent non-pharmacological interventions for NPS in moderate to severe AD. As a secondary objective, the

intervention and pathway complexity were explored by highlighting the characteristics of context, interventions, and participants behind the effects.

2. MATERIALS AND METHODS

This systematic review was informed by the guidelines and standards of the mutually complementary Preferred Reporting Items for Systematic Reviews and Meta-analyses of Complex Interventions (PRISMA-CI; Guise et al., 2017) and the Reporting guideline for Synthesis Without Meta-analysis (Campbell et al., 2020).

2.1. Criteria for considering studies for this review

Both randomized controlled trials (RCTs) and nonrandomized studies of interventions (NRSI) with quantitative designs exploring at least three participants were included in this review. NPS had to be assessed either at baseline and at least one time point after starting intervention or at least three times during both intervention and comparison conditions. Including different study designs allowed the range of non-pharmacological interventions from the real world to be explored too.

Intervention recipients had to be individuals with moderate to severe AD, their caregivers, or both. Studies also investigating mild and different memory disease diagnoses were included if the individuals with moderate to severe AD, their caregivers, or both were analyzed as a subgroup. Participants with AD had to have a diagnosis of probable or possible AD according to primary authors. Participants with AD had to meet the criteria for moderate or severe AD defined by the Mini-mental State Examination with scores ranging from 0 to 20 out of 30 (MMSE; Folstein et al., 1975), the Clinical Dementia Rating with stages 2–3 (CDR; Hughes et al., 1982, as cited in Juva et al., 1995), the Global Deterioration Scale with stages 4–7 (GDS; Reisberg et al., 1982, as cited in Auer & Reisberg, 1997), the Functional Assessment Staging with stages 4–7 (FAST; Sclan & Reisberg, 1992, as cited in Auer & Reisberg, 1997), or any other validated cognitive or functional measurement instrument for the purpose.

Studies were considered for this review if they investigated a psychosocial or environmental nonpharmacological intervention of any type without including any medical treatments. As for comparison control conditions, other nonpharmacological interventions defined above were included as well as “no treatment” or “treatment as usual” conditions. Comparison interventions had to consist of at least one additional non-pharmacological intervention component in relation to the usual

treatment. “Treatment as usual” was taken to mean *context-dependent standard health care with no additional activity*.

The overall and the individual NPS at the end of the interventions were the primary and secondary outcome domains of focus in this review, respectively. The results on the follow-up after the end of the interventions were explored secondarily. The standardized assessment methods for the overall NPS were the primary outcome measurements, while the modified versions of these and the standardized assessment methods for the individual NPS were the secondary ones. The Neuropsychiatric Inventory (NPI; Cummings et al., 1994, as cited in Cummings et al., 1997) was the primary assessment method, while the Behavioral Pathology in Alzheimer’s Disease (BEHAVE-AD; Reisberg et al., 1987, as cited in Reisberg et al., 1997) Rating Scale was the secondary one. In their systematic review and consensus recommendations, Webster et al. (2017) recommend the most commonly used NPI as a best method for assessing overall NPS; it includes both frequency and severity of NPS and it is valid and reliable. The NPI assesses 12 types of individual NPS. The score ranges between 10–120 (involving 10 individual NPS), with a higher score corresponding to greater frequency and severity of overall NPS. According to Webster et al. (2017), the commonly used BEHAVE-AD has sensitivity to change specifically in moderate and severe memory diseases. It assesses seven types of individual NPS. The score ranges between 0–75, with a higher score indicating greater severity of overall NPS.

2.2. Search methods for identification of the studies

First, any recent reviews on this subject were sought in PsycInfo (ovid) and Medline (ovid). Second, only research articles published between January 2009 and the second week of November 2020 in a peer-reviewed journal and written in English were sought via PsycInfo (ovid), Medline (ovid), and CINAHL databases in November 2020. The choice of the beginning of the period was based on the time frames ending during 2008 in the previous study (Kverno et al., 2009) examining nonpharmacological interventions for NPS in advanced memory diseases. Third, the reference lists of both included research articles and identified reviews concerning interventions for NPS in AD during the search process were examined for additional studies. Lastly, the Web of Science cited reference search (timespan: all years - 2020) was conducted for all included research articles and identified reviews to search the articles that referred to them.

In searches, the term “Alzheimer’s disease” was used together with terms relevant to NPS, stage of the AD, and interventions as follows: (Alzheimer’s disease and (behavior* or psychological*

or neuropsychiatric*)).ab. [abstracts] and (moderate or advanced or late stage or severe).af [all fields]. and (therapy or intervention or treat*).ab.

2.3. Data collection and analysis

2.3.1. Data collection and management

Characteristics of included studies were recorded on an electronic data collection form (LimeSurvey GmbH; http://www.limesurvey.org), which is available in Appendix A. Information was collected on any necessary details of study identification and methods, participants, interventions, outcomes, contexts, adverse events, and results.

As for participant characteristics, details of demographic characteristics (gender, age, education, ethnicity, marital status), clinical characteristics (diagnosis and severity of AD, general and social cognitive performance, overall and individual NPS, ADL performance, comorbid conditions, medication, age at onset of and/or duration of AD) and psychosocial characteristics (physical and social environment, QOL, caregiver burden, personality, skill level) were collected. Details of each intervention and comparison conditions were extracted by the Template for Intervention Description and Replication (TIDieR; Hoffmann et al., 2014), which covers the minimum recommended items for describing interventions. More precisely, context, settings, rationale, physical and informational materials, tailoring, modifications, delivery, fidelity, and characteristics of primary intervention components and providers were recorded. When a controlled study was reported in a study, the TIDieR checklist was replicated for each comparison condition. Through the intervention component analysis, each condition was categorized as target intervention, comparison intervention, and usual care control (UCC) condition. Furthermore, each intervention was classified according to its rehabilitative nature and orientation. Where necessary, primary researchers were contacted in order to request additional information.

2.3.2. Summarizing findings and assessing certainty of the evidence

Because the type of effect measure varied across the studies, the findings were summarized by counting the results based on their direction, irrespective of their statistical significance or the size of the effect to keep the clinically important effects (Bushman & Wang, 2009). For each intervention, the direction of each result was categorized as positive (beneficial), negative (deteriorated), or no chance, and the intervention was categorized as beneficial, harmful, or inconclusive, accordingly. If

more than one outcome was reported within an outcome domain and direction of effect varied across multiple outcomes, a similar direction was required from 70 percent of the effects to the rating. For each outcome domain, the binomial test was performed using the direction of results (positive or negative/no chance).

The criteria for assessing the risk of bias (RoB) for the included studies were based on the criteria in Cochrane risk of bias tools for RCTs (Sterne et al., 2019) and NRSIs (Sterne et al., 2016). RoB-judgments for all studies were assigned both at the study level (biases that arise before the start of intervention) and at the outcome level (biases that arise after the start of intervention). Since assessing RoB is specific to a particular result analyzing the specific outcome domain, several RoB-assessments per outcome domain within each study needed to be done in order to answer the review questions as validly as possible. Further, the RoB-judgments were used in assessing the quality of the evidence.

The quality of the evidence was assessed according to the principles of the system for Grading of Recommendations Assessment, Development and Evaluation (GRADE; Schunemann et al., 2013). Factors that determine the quality of evidence as high, moderate, low, or very low are the study design, limitations in study design (RoB), inconsistency of results, indirectness of evidence, imprecision, publication bias, and other modifying factors. The quality of evidence was rated for the primary outcome domain (overall NPS at the end of intervention), across studies. The evidence for GRADE was gathered through the data collection form.

3. RESULTS

3.1. Selection of studies

The database search yielded 1189 references. All references were exported to the web-based bibliography and database manager RefWorks. After the initial removal of duplicates, the titles and abstracts of the remaining 838 articles were reviewed, after which 93 articles remained. In general, the papers excluded at the first stage were not intervention studies, or they were concerned with pharmacological, medical, and other irrelevant interventions. Second, the full text of these remaining 93 articles were reviewed, after which seven articles remained. The excluded articles were mainly concerned with studies focusing on interventions for memory diseases in general without separate subgroup analysis for AD, or they were concerned with AD in general without separate subgroup analysis for moderate to severe stages of AD. Additional cited reference searches through the Web of Science database and the reference lists yielded nine articles. Third, all the remaining 16 articles

were reviewed with the help of a research assistant. Data collection forms with justifications for each study inclusion decision (Appendix 2) were completed. Eventually, 15 articles were included, and one article was excluded after in-depth discussions; these were systematically reported during and after the process. The reason for the exclusion of one study was non-reporting of NPI results (Kurz et al., 2010). The NPI results were not available according to Alexander Kurz (personal communication, February 28, 2020), which was noted as a publication bias at the review level. Two articles (Cox et al., 2011; Cox et al., 2014) were focused on the same study. The final number of the included studies was 14. The PRISMA flow diagram (Moher et al., 2009) of the selection process is shown in Figure 2.

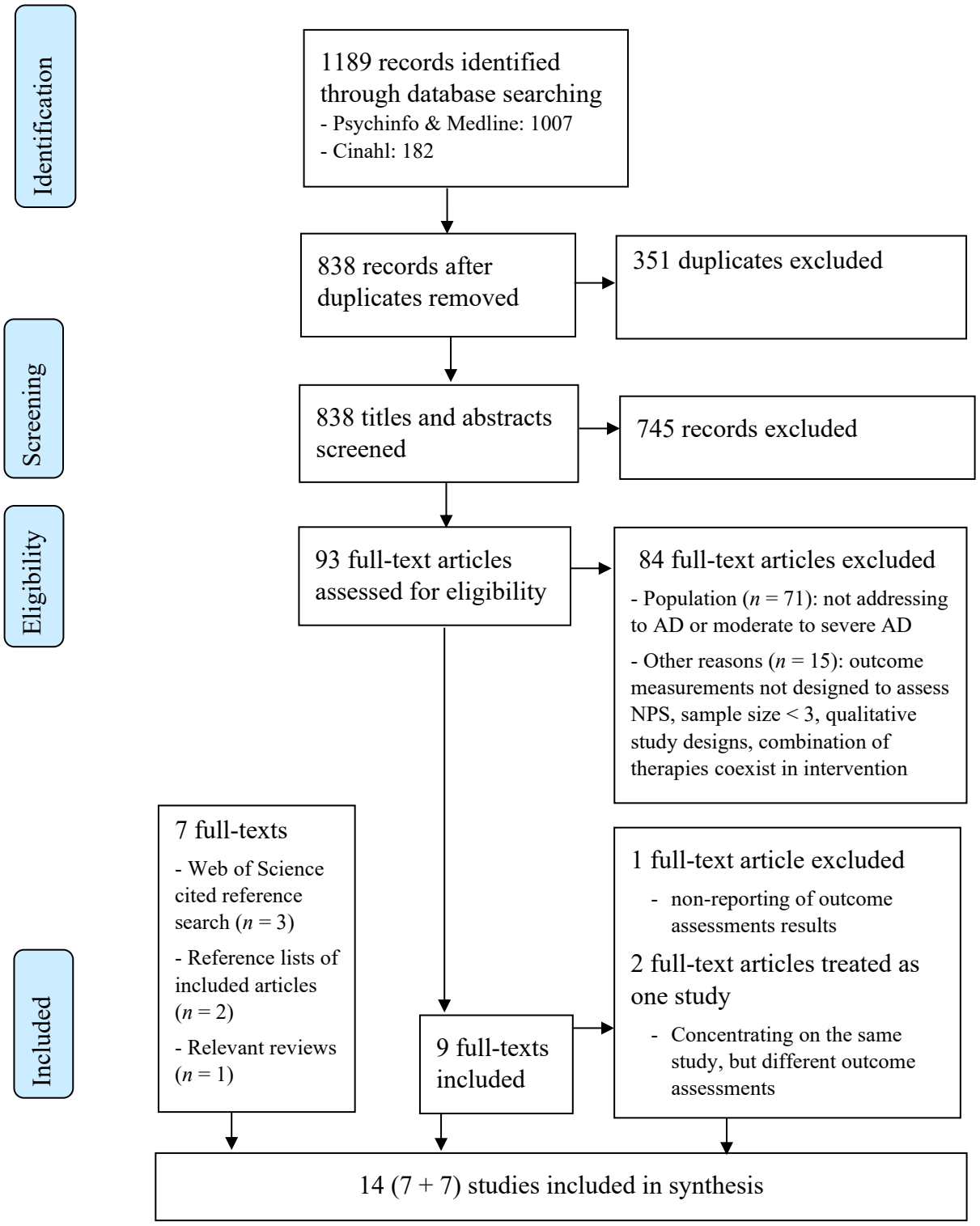

FIGURE 2. The PRISMA flow diagram of studies through the selection process

3.2. Description of studies

Out of all 14 studies, nine (64%) were RCTs and five (36%) were NRSIs. One RCT (Lyu et al., 2018) recruited participants across the spectrum of mild to severe AD, but participants with different severity levels were randomly assigned to the study groups and analyzed as subgroups separately. At present review, the above subgroup analysis was abbreviated to RCTsa. One RCT (van Bogaert et al., 2013) included participants with mild to moderate AD; and in one RCT (Santos et al., 2015), the stage ranged from mild NCD to mild and moderate stages of AD. Both studies analyzed the data of each severity level as separate subgroups. The analyses were treated as NRSIs, because participants were not randomly assigned to the study groups, and they were abbreviated to NRCTsa (van Bogaert et al., 2013) because of nonrandomized controlled trial design and NRTsa (Santos et al., 2015) because of nonrandomized trial design. One observational before-after NRSI (Gómez Gallego & Gómez García, 2017) recruited and separately analyzed participants with mild and moderate AD: the subgroup analysis was abbreviated to NRSIsa. Table 1 presents details of the main characteristics and results of the included 14 studies.

TABLE 1. Characteristics of the 14 studies reviewed

Author(s), year	Country Delivery settings	Study design Eligible study groups	Target if not PWA Eligible *n* (female %) Age: mean/median (SD/Range)	Primary intervention components, tailoring When and how often, delivered individually or in groups	Outcome measures Data collection time points	Outcomes of intervention(s)
1. Aboulafia-Brakha et al., 2014	Brazil; Sao Paulo; SC; outpatient clinic	NRSI; CS Parallel groups: 1. Cognitive-behavioral therapy (CBT) 2. Psycho-education (EDUC)	Target: family CGs *n* (female %): 35 (81) Mean age: CBT: 59.42 (6.67) EDUC: 55.07 (10.68)	CBT: tailored cognitive–behavioral techniques, psychoeducation, and psychosocial support EDUC: receiving information on AD & NPS, not tailored CBT and EDUC: eight 90/60-minute group sessions, once a week, respectively	Overall NPS: BEHAVE-AD T0: Bl T1: week 8 end	Group x time: a significant ($p = 0.001$) effect of time reflecting an improvement in overall NPS in both groups after the intervention.
2. Burns et al., 2011	United Kingdom; MC; long term care sites	RCT Parallel groups: 1. Aromatherapy (AT) 2. Placebo aromatherapy (PA) 3. Placebo (PI)	*n* (female %): 114 (60) Mean age: (63–98) AT: 85.6 (73–98) PA: 84.6 (72–92) PI: 85.1 (63–95)	AT: aromatherapy massage with melissa oil and base lotion, and placebo donepezil tablets, not tailored PA: donepezil medication & placebo aromatherapy massage with sunflower oil and base lotion, not tailored PI: placebo of both, not tailored All interventions: 1–2 min. individual sessions twice a day for 12 weeks	Overall NPS: NPI Agitation: PAS NPI subdomains T0: Bl T1: week 4 T2: week 12 end	No significant ($p > 0.05$) differences between groups in overall NPS and agitation at week 4 and 12 vs Bl, but substantial improvements were found in all 3 groups over 12 weeks. Of all 12 NPI subdomains, only depression improved significantly ($p = .017$) at week 12.
3. Clemént et al., 2012	France; SC; long term care site	RCT Parallel groups: 1. Music (MI) 2. Cooking (CI)	*n* (female %): 14 (55) Mean age: (78–89) MI: 84.4 (81–89) CI: 82.7 (78–89)	MI: alternating between receptive and productive musical activity phases, tailored CI: alternating between receptive and productive cooking activity phases, not tailored MI and CI: 8 two-hour group sessions, twice weekly for 4 weeks	Anxiety: STAI-A T0: 1st day T1: week 2 T2: week 4 end FU1: week 2 FU2: week 4	Anxiety improved significantly ($p < .05$) in MI at T1, T2, FU1 and FU2, and in CI at T1 vs T0.

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TABLE 1. (continued)

Author(s), year	Country Delivery settings	Study design Eligible study groups	Target if not PWA Eligible *n* (female %) Age: mean/median (SD/Range)	Primary intervention components, tailoring When and how often, delivered individually or in groups	Outcome measures Data collection time points	Outcomes of intervention(s)
4. a) Cox et al., 2011 4. b) Cox et al., 2014	Australia SC; long term care site	NRSI; UCS, a single case design One group: live music	*n* (female %): 7 (57) Median age: 77 (70–85)	An informal, participatory live violin recital conducted in the care site wherever the participant was located at the time, not tailored. Three 48 min. individual sessions for 4 weeks; a time (after 2 p.m.) and a day randomly allocated. Each session included 15 min. observation phases before and after the 18 min. musical phase.	4. a) Agitation: a modified CMAI 4. b) Positive behaviors: a modified CMAI Behaviors coded before, during and after the musical phase.	Agitation improved significantly (p = .005) during and after the interventions. Positive behaviors increased significantly (p = .001) during and after the interventions.
5. Gómez Gallego & Gómez García 2017	Spain MC; long term care sites	NRSIsa; UCS, subgroup analysis for moderate AD participants One group: Music therapy	*n* (female %): 17 (71) Mean age: 83.87 (7.75)	Tailored music, dance, and movement ıerapy with social skills training, games, nd drawing Twelve 45 minutes group sessions twice a week for 6 weeks	Overall NPS: NPI Affective symptoms: Overall HADS and the two subdomains depression and anxiety NPI subdomains T0: Bl T1: week 6 end	Overall NPS improved significantly (p = .000). Overall affective symptoms improved significantly (p = .000). HADS subdomains: significant improvements in depression (p = .018) and anxiety (p = .007) at T1 vs T0. NPI subdomains: significant improvements in delusions (p = .024), hallucinations (p = .031), agitation (p = .028), irritability (p = .037) and disinhibition (p = .017) at T1 vs T0.

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TABLE 1. (continued)

Author(s), year	Country Delivery settings	Study design Eligible study groups	Target if not PWA Eligible *n* (female %) Age: mean/median (SD/Range)	Primary intervention components, tailoring When and how often, delivered individually or in groups	Outcome measures Data collection time points	Outcomes of intervention(s)
6. Lyu et al., 2018	China; SC; long term hospital	RCTsa, subgroup analysis (sa) for randomized mod. and sev. AD participants Parallel groups: 1. Music therapy (MT) 2. Lyrics reading exercise (LRE) 3. UCC	*n* (female %): 202 (NA) Mean age: NA	MT: music therapy by singing or listening to their familiar and favorite songs. LRE: reading the lyrics of their familiar and favorite songs. MT and LRE: 30–40 min. group sessions were carried out twice daily with one session in the morning and one session in the afternoon for three months	Overall NPS: NPI T0: Bl T1: 3 months end FU: 3 months	Moderate AD: no significant differences between the groups were found in overall NPS at T1 and FU. Severe AD: overall NPS improved significantly ($p < 0.05$) in MT compared to both groups at T1 and FU.
7. Mossello et al., 2011	Italy; SC; day care centre	NRSI; CS, repeated measures - design Sequential interventions Intervention I: Animal-assisted activities (AAA) Intervention II: Plush-toy (PT)	*n* (female %): 10 (40) Mean age: 79 (69–85)	AAA: an established sequence of tailored actions with the dog PT: an established sequence of tailored actions with the plush dog Study time-schedule: 1. Baseline condition for two weeks 2. PT for three weeks 3. AAA for three weeks AAA and CA: 100 min. group sessions 3 times/week	Overall NPS: NPI Agitation: CMAI, ABMI Depression: CSDD NPI subdomains T0: before PT T1: PT end (at 3 weeks) T2: AAA end (at 6 weeks) ABMI: observations periods during CA and AAA	No significant changes in overall NPS and agitation (CMAI, ABMI) over time. A trend for an improvement in depression (CSDD) was found after AAA (p for trend = .035), ns. in post-hoc analysis. NPI subdomains: only results for anxiety were reported which improved significantly ($p = .04$) between T1 and T2.

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TABLE 1. (continued)

Author(s), year	Country Delivery settings	Study design Eligible study groups	Target if not PWA Eligible n (female %) Age: mean/median (SD/Range)	Primary intervention components, tailoring When and how often, delivered individually or in groups	Outcome measures Data collection time points	Outcomes of intervention(s)
8. Narme et al., 2014	France; SC; long term care site	RCT Parallel groups: 1. Music (MI) 2. Cooking (CI)	n (female %): 48 (86) Mean age: MI: 86.7 (6.4) CI: 87.5 (6.0)	MI: alternating between receptive and productive musical activity phases, not tailored CI: alternating between receptive and productive cooking activity phases, tailored MI & CI: One-hour group sessions, twice a week, for a period of 4 weeks	Overall NPS: NPI Agitation: CMAI Anxiety: STAI-A T0: 1 week before T1: 2 weeks T2: 4 weekend FU1: 2 weeks FU2: 4 weeks	Overall NPS improved significantly: in MI at T1 (p = .001), T2 (p = .04), FU1 (p = .03), FU2 (p = .04) and in CI at T1 (p = .04), T2 (p = .008) vs T0. Agitation improved significantly: in MI at T1 (p = .004) and in CI at T1 (p = .005), T2 (p = .001), FU1 (p = .003), FU2 (p = .007) vs T0. Anxiety improved significantly: in MI at T1 (p = .02) and in CI at T1 (p = .005), T2 (p = .009), FU1 (p = .008) vs T0.
9. Pedrinolla et al., 2019	Italy; SC; long term care site	RCT Parallel groups: 1. Therapeutic Garden (TG) 2. Standard Environment (SE)	n (female %): 163 (74) Mean age: TG: 76.4 (4.3) SE: 78.6 (4.7)	TG: Free interaction with natural environment in the indoor TG, tailored SE: Free interaction with a standard AD unit environment, tailored TG & SE: Two-hour group sessions; 5 times a week for 6 months	Overall NPS: NPI T0: Bl T1: 6 months end	Group x time interactions: overall NPS improved significantly in TG compared to SE (p < .001) at T1. Additional factors sex and baseline MMSE: no influence

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TABLE 1. (continued)

Author(s), year	Country Delivery settings	Study design Eligible study groups	Target if not PWA Eligible *n* (female %) Age: mean/median (SD/Range)	Primary intervention components, tailoring When and how often, delivered individually or in groups	Outcome measures Data collection time points	Outcomes of intervention(s)
10. Sakamoto et al., 2013	Japan; MC; long term hospital & assisted living facilities	RCT Parallel groups: 1. Interactive music (IM) 2. Passive music (PM) 3. Silent environment (SE)	*n* (female %): 39 (82) Mean age: IM: 81.2 (7.5) PM: 81.1 (11) SE: 81 (8.3)	IM: listening to individualized music, engaging in musical performance with CG PM: listening to the individualized music without direct interaction SE: spending time with CG without direct interaction. not tailored All interventions: 10 individual sessions, 30 min. at 10:00–11:00 am once a week	NPS subdomains: BEHAVE-AD T0: Bl: two weeks prior to the study T1: 10 weekend FU: 3 weeks	Significant improvements were found at T1 vs T0: Delusions: IM $p = .01$; PM $p = .03$ Activity disturbances: IM $p = .01$ Aggressiveness: IM $p = .01$ Affective disturbances: IM $p = .02$; PM $p = .02$ Anxieties and phobias: IM $p = .01$; PM $p = .02$ FU vs. T1 IM: hallucinations, activity disturbances and aggressiveness increased significantly ($p < .05$). IM and PM: delusions, affective disturbances and anxieties and phobias increased significantly ($p < .05$)
11. Santos et al., 2015	Brazil; SC; rehab. unit: day-hospital facility	RCT (NRTsa) Nonrandomized trial Subgroup (sa) analysis for mod. AD participants One group: Multimodal rehabilitation (MR)	Target: AD patients and their CGs AD patients: *n* (female %): 13 (77) Mean age: 77	MR for AD patients: cognitive stimulation, rehabilitation, and training; speech, art, occupational and physical therapy; physical training, not tailored For CGs: psychoeducation and support MR: 24 five-hour group sessions, twice a week for 12 weeks. Sessions lasted from 9:00 a.m. to 3:30 p.m. (lunch and refreshments: 90 min.) Interventions for caregivers: twice a week	Depression: GDS T0: Bl T1: week 12 end	No differences were found in depression ($p = .249$) at week 12 vs Bl.

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TABLE 1. (continued)

Author(s), year	Country Delivery settings	Study design Eligible study groups	Target if not PWA Eligible *n* (female %) Age: mean/median (SD/Range)	Primary intervention components, tailoring When and how often, delivered individually or in groups	Outcome measures Data collection time points	Outcomes of intervention(s)
12. Van Bogaert et al., 2013	Belgium; MC; long term hospital, rehab. centre & day care centre	RCT (NRCTsa) Nonrandomized controlled trial Subgroup analysis (sa) for mod. AD participants Parallel groups: 1. Reminiscence (RT) 2. UCC	*n* (female %): 39 NA Mean age: NA	The standard process component: each session was structured with an introduction and round off phase and a reminiscence phase; standardized topic was explored each week (family, profession, holiday, and games), tailored Two 45-minute individual sessions twice a week for 4 weeks	Overall NPS: NPI NPI subdomains Depression: CSDD, GDS T0: Bl T1: 4-week endpoint	Between groups: Significant differences were found only in depression (GDS) at week: RT group had better ($p < .01$) GDS delta scores than UCC group. Within groups: Of all NPI subdomains, only results for dysphoria, and appetite and eating were reported: both were reported to have significant improvements at week 4 vs T0.
13. Venturelli et al., 2012	Italy; SC; long-term care site	NRSI repeated measures -design Sequential interventions Intervention I: Adapted games (AG) Intervention II: Foot bath and massage (FB)	*n* (female %): 28 (79 %) Mean age: 83 (76–87)	AG: ball games sitting in standard armchairs or wheelchairs and forming a circle. The kinesiologist controlled the AG group from the center of the circle, tailored FB: Individual aromatherapeutic foot bath and massage sitting in standard armchairs or wheelchairs, not tailored Each participant completed two 30 min. sessions 2 times on different days; 1 week of washout between interventions	Agitation: ABRS T1: observation period 1 hour before each AG and PL sessions T2: observation period 1 hour after each AG and PL sessions	Group x time interactions: The average of agitated behaviors decreased significantly (60 %; $p < .05$) only in AG group at T2 vs T1 and compared to FB group at T2.

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TABLE 1. (continued)

Author(s), year	Country Delivery settings	Study design Eligible study groups	Target if not PWA Eligible *n* (female %) Age: mean/median (SD/Range)	Primary intervention components When and how often, delivered individually or in groups	Outcome measures Data collection time points	Outcomes of intervention(s)
14. Venturelli et al., 2016	Italy; SC; long term care site	RCT Parallel groups: 1. Aerobic exercise (AE) 2. Cognitive training (CT) 3. AE + CT 4. UCC	*n* (female %): 80 (72) Mean age: AE: 84 (7) CT: 86 (9) AE + CT: 85 (8) NT: 84 (10)	AE: tailored walking exercise with CG along the hallway, maintaining the fastest walking speed possible, interacting with CG CT: Two members of the research team presented and asked the same information (reality orientation therapy; ROI), tailored AE + CT: during walking, ROI was delivered by the CG, tailored All interventions: 1-hour individual sessions before the sunset, 5 days a week for 3 months	Overall NPS: NPI Agitation: ABS T0: Bl T1: 3 months end 2 days preintervention and 2 days postintervention, in the morning (10 a.m.) and at the time corresponding to sundown.	Group x time interactions: Agitation symptoms decreased significantly ($p < .05$) in AE & AE + CT after 12 weeks vs. baseline (sundown). No changes in CT and in NT. Overall NPS decreased significantly ($p < .05$) in AE & AE + CT after 12 weeks vs. baseline (sundown). No changes in CT and in NT.

Abbreviations: AAA = animal-assisted activities; ABMI = Agitated Behavior Mapping Instrument; ABS = Agitated Behavior Scale; ABRS = Agitated Behavior Rating Scale; AD = Alzheimer' s disease; AE = aerobic exercise; AG = adapted games; AM = active music intervention; AT = aromatherapy; Bl = baseline; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Scale; CI = cooking intervention; CDR = Clinical Dementia Rating Scale; CG = caregiver; CMAI = Cohen Mansfield Agitation Index; CS = controlled study; CSDD = Cornell Scale for Depression in Dementia; EDUC = psychoeducation; FB = foot bath; FU = follow-up; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; IM = Interactive music intervention; LRE = lyrics reading exercise; MC = multi centre; MF = music facilitator; MI = Music intervention; MT = Music therapy; MMSE = Mini-Mental State Examination; MR = multimodal rehabilitation; NA = not available; n = number of participants; NPI = Neuropsychiatric Inventory; NPS = neuropsychiatric symptoms; NRSI = non-randomized studies of interventions; PAS = Pittsburgh Agitation Scale; PI = placebo intervention; PT = plush-toy intervention; PM = passive music intervention; PWA = person with Alzheimer's disease; PA = placebo aromatherapy; RT = reminiscence therapy; RCT = randomized controlled trial; sa = subgroup analysis; SC = single centre; STAI-A = StateTrait Anxiety Inventory for Adults; T = time; UCC = usual care control; UCS = uncontrolled study

Out of 11 controlled intervention studies, eight compared the target intervention to the comparison intervention(s) only. In two RCTs (Lyu et al., 2018; Venturelli et al., 2016), the target and the comparison interventions were compared also to the usual care control (UCC) condition. The NRCTsa (Van Bogaert et al., 2013) was the only study comparing the target intervention exclusively to UCC. The three uncontrolled study designs were carried out in NRSI (Cox et al., 2011), NRSIsa (Gómez Gallego & Gómez García, 2017), and in NRTsa (Santos et al., 2015).

Adherence to the interventions was presented as a percentage in three RCTs (Burns et al., 2011; Pedrinolla et al., 2019; Venturelli et al., 2016), including eight interventions (mean: 65%, range: 50–85%). Interventions were videotaped in three studies. In one of these studies (Sakamoto et al., 2013), the number of minutes of behavior indicating responding to two interventions were observed and calculated from the video recordings. Most participants showed positive engagement in passive music intervention more than half the time and with interactive music intervention most of the time. The periods were significantly ($p < .05$) longer in the interactive group compared to the passive group. In one NRSI (Cox et al., 2011), the type and frequency of behaviors were observed and calculated from the video recordings. All participants showed positive engagement in intervention reaching significance ($p < .05$) for 9 of the 16 behaviors assessed. One RCT (Lyu et al., 2018) and two NRSIs (Gómez Gallego & Gómez García, 2017; Venturelli et al., 2012) described narratively that participants showed high positive engagement in all their five interventions.

Three studies addressed simultaneous nonpharmacological treatments. In Lyu et al. (2018), Mossello et al. (2011), and Venturelli et al. (2016), participants were reported to have received routine nonpharmacological treatment during the study. Only Venturelli et al. (2016) addressed whether the four groups differed in exposure to simultaneous rehabilitation ($p = 0.8$). The simultaneous medication was stated to have remained constant for the duration of the study in seven studies (Clemént et al., 2012; Cox et al., 2011; Lyu et al., 2018; Mossello et al., 2011; Narme et al., 2013; Sakamoto et al., 2013; Venturelli et al., 2016). Pedrinolla et al. (2019) studied the effect of the environmental intervention on antipsychotic medication, but the dosages of all other drugs were kept stable during the study. Burns et al. (2011) only included participants who had not used the anticholinesterase and/or antipsychotic drugs for at least two weeks at baseline. Similarly, only participants who had not commenced any new treatment affecting agitation over the past four weeks were included in Cox et al. (2011). In five studies, 24% (Gómez Gallego & Gómez García, 2017), 39% (Pedrinolla et al., 2019), 43% (Cox et al., 2011), 50% (Venturelli et al., 2016), and 55% (Venturelli et al., 2012) of participants were reported to have been treated with antipsychotic drugs.

At the study level, the overall risk of bias was classified as high in four RCTs (Burns et al., 2011; Clément et al., 2012; Narme et al., 2013; Sakamoto et al., 2013). Two RCTs (Pedrinolla et al.,

2019; Venturelli et al., 2016) and one RCTsa (Lyu et al., 2018) were rated as having some concerns of risk. Two NRSIs (Cox et al., 2011; Gómez Gallego & Gómez García, 2017) and one NRTsa (Santos et al., 2015) were classified as having critical overall risk of bias, and serious risk were rated for three NRSIs (Aboulafia-Brakha et al., 2014; Mossello et al., 2011; Venturelli et al., 2012) and one NRCTsa (Van Bogaert et al., 2013). Appendices B and C present a summary of the judgments about overall risk of bias and each risk of bias domain for RCTs and NRSIs, respectively.

3.3. Interventions for participants with Alzheimer's disease

3.3.1. The range and effects of interventions

Table 2 shows the range of target and comparison interventions in the intervention categories by study designs. Intervention effects based on their direction are shown by outcome domains.

TABLE 2. The range of interventions in the intervention and study design categories and intervention effects (based on their direction) by outcome domains at the end of the interventions (from four weeks to three months) and after a follow-up (from three weeks to three months)

Interventions	Design	First author year	Outcome domains												
			Overall	AMB	Agit.	Anx.	Apathy	Delus.	Depr.	Disinh.	Euph.	Hallucin.	Irritab.	Sleep	Eating
Stimulation															
Music															
Target +	RCT	Clemént 2012	na	na	na	**1***, **1***	na	na	na	na	na	na	na	na	na
Target +		Narme 2014	**1***, **1***	na	1, 1	1, -0	na	na	na	na	na	na	na	na	na
Target +		Sakamoto 2013	**1***†	**(1*, -0*)**	**(1*, -0*)**	**(1*, -0*)**	na	**(1*, -0*)**	**(1*, -0*)**	na	na	(1, **-0***)	na	(0, 0)	na
Comp. +		Sakamoto 2013	1†	(1, -0)	(0, 1)	**(1*, -0*)**	na	(1, **-0***)	**(1*, -0*)**	na	na	(1, **-0**)	na	(-0, 1)	na
Target +	RCTsa	Lyu 2018	Mod. [a]1, 1 Sev. [a]1, 1	na	na	na	na	na	na	na	na	na	na	na	na
Target +	NRSI	Cox 2011	na	na	1**	na	na	na	na	na	na	na	na	na	na
Target +	NRSIsa	Gómez Gallego 2017	**1*****	(1)	**(1**)**	**1**** (1)	(1)	**(1*)**	**1*** (1)	**(1*)**	(1 nr)	**(1*)**	**(1*)**	(1 nr)	(1 nr)
Exercise															
Target +	RCT	Venturelli 2016	[b]**1***	na	[b]**1***	na	na	na	na	na	na	na	na	na	na
Target +	NRSI	Venturelli 2012	na	na	[b]**1***	na	na	na	na	na	na	na	na	na	na
Relaxation															
Comp. +	RCT	Burns 2011	1	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)
Comp. +		Burns 2011	1	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)
Comp. +	NRSI	Venturelli 2012	na	na	[b]**1***	na	na	na	na	na	na	na	na	na	na
Aromatherapy															
Target +	RCT	Burns 2011	1	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)	([a]1)
Animal															
Target +	NRSI	Mossello 2011	1	(1 nr)	1 (1 nr)	(1)	(1 nr)	(1 nr)	1 (1 nr)	(1 nr)	(1 nr)	(1 nr)	(1 nr)	(1 nr)	(1 nr)
Plush-toy															
Comp. +	NRSI	Mossello 2011	1	(1 nr)	1 (1 nr)	(-0)	(1 nr)	(1 nr)	0 (1 nr)	(1 nr)	(1 nr)	(1 nr)	(1 nr)	(1 nr)	(1 nr)

(continued on next page)

TABLE 2. (continued)

Interventions	Design	First author year	Outcome domains: Overall	AMB	Agit.	Anx.	Apathy	Delus.	Depr.	Disinh.	Euph.	Hallucin.	Irritab.	Sleep	Eating
Stimulation															
All			**11/11*****	(6/6*)	**7/7**** (5/6)	3/3 (7/8*)	(4/4)	(6/6*)	2/3 (6/6*)	(4/4)	(3/3)	(6/6*)	(4/4)	(3/5)	(3/3)
	RCT/ RCTsa		**8/8****	(5/5*)	2/2	2/2*	(3/3)	(5/5)	(5/5*)	(3/3)	(3/3)	(5/5*)	(3/3)	(3/5)	(3/3)
Behavior															
Cooking															
Comp. +	RCT	Clemént 2012	na	na	na	1, -0	na	na	na	na	na	na	na	na	na
Comp. +		Narme 2014	**1****, **1**	na	**1****, **1****	**1****, **1**	na	na	na	na	na	na	na	na	na
Emotion															
Reminiscence															
Target +	NRCTsa	Van Bogaert 2013	[a]1	(1 nr)	(1 nr)	(1 nr)	(1 nr)	(1 nr)	[a]**1**** [a]1 **(nr)**	(1 nr)	(1 nr)	(1 nr)	(1 nr)	(1 nr)	**(nr)**
Lyrics reading															
Comp. +	RCTsa	Lyu 2018	[a]1, 1	na	na	na	na	na	na	na	na	na	na	na	na
Cognition															
Cogn. training															
Comp. -	RCT	Venturelli 2016	[b]0	na	[b]**-** 0	na	na	na	na	na	na	na	na	na	na
Stim. & cogn.															
Exercise & reality orient															
Comp. +	RCT	Venturelli 2016	[b]**1***	na	[b]**1***	na	na	na	na	na	na	na	na	na	na
Multimodal stimulation															
Target +	NRTsa	Santos 2015	na	na	na	na	na	na	1	na	na	na	na	na	na
Environmental															
Therapeutic garden															
Target +	RCT	Pedrinolla 2019	[b]**1*****	na	na	na	na	na	na	na	na	na	na	na	na

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TABLE 2. (continued)

Interventions	Design	First author year	Outcome domains												
			Overall	AMB	Agit.	Anx.	Apathy	Delus.	Depr.	Disinh.	Euph.	Hallucin.	Irritab.	Sleep	Eating
Silent															
Comp. -	RCT	Sakamoto 2013	-0	(**-0***, **-0**)	(-0, 1)	(-0, 1)	na	(1, -0)	(**-0***, 0)	na	na	(-0, 1)	na	(-0, 1)	na
Standard															
Comp. -	RCT	Pedrinolla 2019	[b]-0	na	na	na	na	na	na	na	na	na	na	na	na
All			**16/19****	(6/7)	**9/10**** (5/7)	**5/5*** (8/9)	(4/4)	(7/7**)	4/5 (6/7)	(4/4)	(3/3)	(6/7)	(4/4)	(4/6)	(3/3)
	RCT/ RCTsa:		**12/15***	(5/6)	4/5	2/3	(3/3)	3/3 (5/5)	(5/6)	(3/3)	(3/3)	(5/6)	(3/3)	(4/6)	(3/3)

Abbreviations: ABM = aberrant motor behavior; n = number of persons with Alzheimer's disease; na = not available; NPS = neuropsychiatric symptoms; nr = not reported; NRCT = non-randomized controlled trial; NRSI = nonrandomized studies of interventions; NRT = non-randomized trial; RCT = randomized controlled trial; sa = subgroup analysis, 1 = positive (beneficial), -0 = negative (deteriorated)

Individual symptoms measured as subdomains are shown in parentheses.

+ = beneficial, - = harmful

* = $p < .05$, ** = $p < .01$, *** = $p < .001$

[a] = In the primary study, statistical significance reported only for difference in change between control and intervention group.

[b] = In the primary study, statistical significance reported for group x time.

† = Baseline and endpoint scores were reported only for individual NPS.

‡ = gender of the participants completing the assessment at week four during the intervention

Thirteen studies (93%) recruited persons with AD (PWA; $n = 774$). These studies introduced a total of 25 interventions (13 target interventions, 12 comparison interventions) and three UCCs. According to primary intervention components (Table 1), interventions were classified as psychosocial ($n = 22$; 88%) and environmental ($n = 3$; 12%) interventions. Psychosocial interventions were further divided into stimulation-oriented ($n = 15$; 60%), behavior-oriented ($n = 2$; 8%), emotion-oriented ($n = 2$; 8%), cognition-oriented ($n = 1$; 4%), and stimulation- and cognition oriented ($n = 2$; 4%) approaches.

Out of all interventions, 22 (88%) were classified as beneficial and three (12%) as harmful (Table 3). As for psychosocial interventions for AD participants, all but one (95%) were classified as beneficial. The only cognition-oriented intervention, the cognitive training (comparison) in Venturelli et al. (2016) RCT, was harmful: overall NPS (NPI) had not changed, and agitation (ABS) had deteriorated without reaching significance. Regarding the three environmental interventions, one of them was beneficial: the effects of the therapeutic garden (target) on overall NPS (NPI) had reached significance of $p < .001$ (Pedrinolla et al., 2019). The standard environment (comparison) in the same study was harmful; overall NPS had deteriorated without reaching significance. The silent environment (comparison) in Sakamoto et al. (2013) RCT was also harmful. It was the only nonpharmacological intervention that reported significant harmful effects; all but one BEHAVE-AD subdomains had deteriorated, reaching significance in ABM ($p < .01$) and depression ($p < .02$). Only delusions had slightly improved without reaching significance.

As for the three studies using UCC group, Venturelli et al. (2016) showed in their RCT that NPS and agitation had decreased significantly in the aerobic exercise (AE) group and in the AE + cognitive training group at the end of the interventions. In the cognitive training group, no changes were observed in NPS, and a deterioration without reaching significance was recorded in agitation. In the UCC group, no changes were observed. Lyu et al. (2018) showed in their RCT that NPS decreased slightly more in the moderate AD music group than in the moderate lyrics and UCC groups. In the severe music group, NPS decreased significantly more compared to both groups. In Van Bogaert et al. (2013) NRCTsa, depression decreased significantly more in the reminiscence group compared to the UCC group when using GDS assessment method, while the decline did not reach statistical significance when using CSDD. NPS decreased slightly more in the moderate AD reminiscence group than in the UCC group.

Based on the direction of effects, there was enough evidence to suggest that the nonpharmacological interventions had a beneficial effect on overall NPS (16/19, 84 %, $p < .01$). As for the 15 interventions carried out in RCTs, the overall quality for effects on overall NPS at end of treatment was high (Appendix D). Regarding the four NRSIs/others, the overall quality for effects on NPS was very low, downgraded for limitations in study design and imprecision. The beneficial effect

on NPS subdomains was found in both agitation (9/10, 90%, $p < .01$) and anxiety (5/5, 100%, $p < .05$). Further, delusions (7/7, 100%, $p < .01$) improved when measured as a subscale. On closer inspection of intervention categories, evidence was only enough for stimulation-oriented interventions to suggest that they had a beneficial effect on overall NPS (11/11, 100%, $p < .001$) and agitation (7/7, 100%, $p < .01$). Measured as subscales, AMB (6/6, 100%, $p < .05$), delusions (6/6, 100%, $p < .05$) and hallucinations (6/6 100%, $p < .05$) improved at the end of the interventions.

The two RCTs comparing the intervention effects after the four-week follow-up time versus baseline found that the beneficial effects of musical interventions were still significant ($p < .05$) in overall NPS (Narme et al., 2014) and in anxiety (Clement et al., 2012). Furthermore, the beneficial effects of cooking intervention were still significant in agitation (Narme et al., 2014). Sakamoto et al. (2013) compared the effects of the two music interventions after the three-week follow-up time versus intervention endpoint and found that most subdomains were significantly deteriorated ($p < .05$).

Of the five studies that reported adverse events, they were not observed in Pedrinolla et al. (2019), in Venturelli et al. (2016) RCTs, and in Gómez Gallego and Gómez García (2017) NRSIsa. In Burns et al. (2011) RCT, 27 adverse events were counted, and nine participants withdrew from the study because of agitation. In Venturelli et al. (2012) NRSI, two participants experienced anxiety and discomfort during the exercise intervention, and two participants experienced some discomfort during the foot bath relaxation as well.

3.3.2. Interventions and participants behind the effects

According to the goals, techniques, and theories of the primary intervention components, psychosocial interventions were classified as leisure facilitation interventions (LFIs), recreational therapies (RTs), and psychotherapeutic interventions. Table 3 shows these classifications and main effects of interventions, as well as the number, gender, the AD stage and baseline and endpoint overall NPS of PWA involved in all interventions.

TABLE 3. The classifications and main effects of interventions and basic characteristics of the participants with Alzheimer's disease

Interventions Study: first author, year, design	Leisure–therapeutic Receptive–productive Interactiveness	*n*	Gender: *n* (%)	AD stage Baseline Overall NPS	Direction of effect Endpoint Overall NPS
Stimulation					
Music					
Target Clément 2012, RCT	Recreational therapy Productive Interactive	5	Female: 4 (80) Male: 1 (20)	Severe Behave-AD 11.0 (4-19)	**Anxiety. 1*** NA
Target Narme 2014, RCT	Recreational therapy Productive Interactive	18	Female: 15 (83) Male: 3 (17)	Moderate to severe Behave-AD 16.7 (17.9)	**NPS 1*** 8.7 (16.4) Agitation 1 Anxiety 1
Target Sakamoto 2013, RCT	Recreational therapy Productive Interactive	13	Female: 11 (85) Male: 2 (15)	Severe NA†	NPS 1*† NA†
Comparison Sakamoto 2013, RCT	Leisure facilitation Receptive Noninteractive	13	Female: 10 (77) Male: 3 (23)	Severe NA†	NPS 1† NA†
Target Lyu 2018, RCT	Recreational therapy Receptive/productive, Interactive	67	NA	Moderate (n = 34) NPI 25.68 (12.74) Severe (n = 33) NPI 36.87 (16.85)	NPS[a] 1 20.12 (11.53) NPS[a] 1 26.57 (10.35)
Target Cox 2011, NRSI	Leisure facilitation Receptive Participatory	7	Female: 4 (57) Male: 3 (43)	Moderate to severe NA	**Agitation 1*** NA
Target Gómez Gallego 2017	Recreational therapy Productive Interactive	17	Female: 12 (71) Male: 5 (29)	Moderate NPI 22 (25.59) 22 25.59	**NPS 1***** 9.75 (5.07) **Depression 1*** **Anxiety 1****
Exercise					
Target Venturelli 2016, RCT	Recreational therapy Productive Interactive	20	Female: 15 (75) Male: 5 (25)	Mod. to moderately sev. NPI NA	**NPS[b] 1*** NA **Agitation[b] 1***
Target Venturelli 2012, NRSI	Recreational therapy Productive Participatory	28	Female: 22 (79) Male: 6 (21)	Moderate to severe NA	**Agitation[b] 1*** NA
Relaxation					
Comparison Placebo aromatherapy Burns 2011, RCT	Recreational therapy Receptive Participatory	37	Female: 15 (64) Male: 16 (52)‡	Severe NPI NA	NPS[a] 1 –2.0 (–7.2, 3.2)
Comparison Placebo of both Burns 2011, RCT	Recreational therapy Receptive Participatory	39	Female: 22 (48) Male: 11 (36) ‡	Severe NPI NA	NPS[a] 1 –10.0 (–17.2, –3.0)
Comparison Venturelli 2012, NRSI	Recreational therapy Receptive Participatory	28	Female: 22 (79) Male: 6 (21)	Moderate to severe NA	Agitation[b] 1 NA

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TABLE 3. (continued)

Interventions Study: first author, year, design	Leisure–therapeutic Receptive–productive Interactiveness	*n*	Gender: *n* (%)	AD stage Baseline overall NPS	Direction of effect Endpoint overall NPS
Aromatherapy					
Target Burns 2011, RCT	Recreational therapy Receptive Participatory	38	Female: 2 (66) Male: 11 (34)‡	Severe NPI NA	NPS[a] 1 –7.2 (–12.6, –1.7)
Animal					
Target Mossello 2011, NRSI	Recreational therapy Productive Interactive	10	Female: 4 (40) Male: 6 (60)	Moderate to severe 21.4 (11.5)	NPS 1 21.3 (10.3)
Plush-toy					
Comparison Mossello 2011, NRSI	Recreational therapy Productive Interactive	10	Female: 4 (40) Male: 6 (60)	Moderate to severe 22.2 (10.0)	NPS 1 21.4 (11.5)
Behavior					
Cooking Comparison Clément 2012, RCT	Recreational therapy Productive Interactive	6	Female: 2 (33) Male: 4 (67)	Moderately sev. to sev, Behave-AD 5.8 (2-13)	Anxiety 1 NA
Comparison Narme 2014, RCT	Recreational therapy Productive Interactive	19	Female: 17 (89) Male: 2 (11)	Moderate to severe Behave-AD 12.5 (15.3)	**NPS 1**** 3.3 (4.7) **Agitation 1**** **Anxiety 1****
Emotion					
Reminiscence Target Van Bogaert 2013, NRCTsa	Therapy Productive Interactive	22	NA	Moderate NPI 7.59 (9.7)	NPS 1 4.55 (4.9) **Depression 1**** Depression 1
Lyrics reading					
Comparison Lyu 2018, RCTsa	Recreational therapy Receptive/productive Interactive	68	NA	Moderate NPI 23.95 (13.32) Severe NPI 36.85 (17.63)	NPS[a] 1 M. 21.36 (11.77) S 31.27 (15.36)
Cognition					
Cognitive training Comparison Venturelli 2016, RCT	Therapy Productive Interactive	20	Female: 16 (80) Male: 4 (20)	Mod. to moderately sev. NPI NA	NPS[b] 0 NA Agitation[b] -0
Stimulation & cognition					
Exercise & cognitive training Comparison Venturelli 2016, RCT	Recreational therapy Productive Interactive	20	Female: 14 (70) Male: 6 (30)	Mod. to moderately sev. NPI NA	**Total NPS[b] 1*** NA **Agitation[b] 1***
Multimodal stimulation Target Santos 2015, NRTsa	Recreational therapy Productive Interactive	13	Female: 10 (77) Male: 3 (23)	Moderate NA	Depression 1 NA
Environmental					
Therapeutic garden Target Pedrinolla 2019, RCT	Other	82	Female: 60 (73) Male: 22 (27)	Moderate to severe NPI 67.7 (19.0)	**Total NPS[b] 1*** 38.7 (14.3)

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TABLE 3. (continued)

Interventions Study: first author, year, design	Leisure–therapeutic Receptive–productive Interactiveness	*n*	Gender: *n* (%)	AD stage Baseline overall NPS	Direction of effect Endpoint overall NPS
Silent with caregiver Comparison Sakamoto 2013, RCT	Environmental	13	Female: 11 (85) Male: 2 (15)	Severe NA†	Total NPS -0† NA†
Standard with manager Comparison Pedrinolla 2019, RCT	Environmental	81	Female: 61 (75) Male: 20 (25)	Moderate to severe NPI 66.4 (16.5)	Total NPS[b] -0 70.0 (15.6)

Abbreviations: AD = Alzheimer's disease; n = number of persons with Alzheimer's disease; NA = not available; NPS = neuropsychiatric symptoms; NRCT = non-randomized controlled trial; NRSI = nonrandomized studies of interventions; NRT = non-randomized trial; RCT = randomized controlled trial; sa = subgroup analysis, 1 = positive (beneficial), -0 = negative (deteriorated)

* = $p < .05$, ** = $p < .01$, *** = $p < .001$

[a] = In the primary study, statistical significance reported only for difference in change between control and intervention group.

[b] = In the primary study, statistical significance reported for group x time.

† = Baseline and endpoint scores were reported only for individual NPS.

‡ = gender of the participants completing the assessment at week four during the intervention

Most of the interventions were classified as recreational therapies, further categorized as receptive, productive, receptive/productive, interactive, participatory, and noninteractive. The two leisure facilitation interventions (stimulation-oriented music interventions) were further categorized as receptive, while the two therapeutic interventions (emotion-oriented reminiscence, cognition-oriented cognitive training) were categorized as productive.

All interventions were informed either by general rationales or specific theories along with general rationales. The primary goal of the leisure facilitation interventions was eliciting positive emotions and enjoyment, and they were delivered by the researchers themselves or therapists and nurses trained by research staff. Recreational and therapeutic interventions had the aim of accomplishing health- and behavior-related goals through specific intervention models or protocols and guidance and monitoring of specialists. The recreational therapies were provided by the researchers themselves, specialists (music therapists, kinesiologists) and nurses trained by specialists or research staff. Research staff and specialists delivered the therapeutic interventions.

The intervention effects on overall NPS were analyzed at the end of 19 interventions that included 607 AD participants. Table 4 shows the number of interventions according to their rehabilitative nature (leisure facilitation interventions, recreational therapies, psychotherapies, and other interventions) and effects (beneficial, inconclusive, harmful) on overall NPS, as well as the number of AD participants included in each intervention type. (See Table 2 for all the specific intervention categories, interventions, and citations.)

TABLE 4. Interventions according to their rehabilitative nature and effects on overall NPS

		Effects			AD participants
	Rehabilitative nature	Beneficial	Inconclusive	Harmful	
Intervention types	Leisure facilitation	1 (7)	-	-	13 (2)
	Recreational therapy	13 (87)	-	-	445 (73)
	Psychotherapy	1 (7)	-	1 (33)	42 (7)
	Environmental	1	-	2 (67)	107 (18)
Total	**19**	**16**	**-**	**3**	**607**

The 13 interventions classified as recreational therapies, the leisure facilitation intervention, the psychotherapy, and the environmental intervention were behind the beneficial effects on overall NPS. The cognition-oriented intervention classified as psychotherapy and two environmental interventions (standard and silent environments plus presence of deliverer) were responsible for the harmful effects on overall NPS.

Regarding the demographic, clinical, and psychosocial characteristics of AD participants, all the extracted characteristics are described if at least one RCT/RCTsa or two other studies reported them. The 10 studies that reported the number of participants eligible for the review in the gender categories showed 361 (71%) women and 146 men (29%). Participants' average age ranged from 76.4–87.5 years in the nine studies that reported age. Two studies extracted the number of years of education, with the average of 7 years (Clemént et al., 2012) and 8.5 years (Narme et al., 2014).

Moreover, clinical characteristics were assessed and reported variously across the studies. In all studies, the AD diagnosis was reported to be based either on formal AD criteria or other formal confirmations. The mean duration of AD at baseline was 7.5 years in the one study (Pedrinolla et al., 2019) that extracted the data. ADL performance was assessed using Barthel Index (BI; Mahoney & Barthel, 1965) in five studies. BI scores range between 0–99, with lower scores corresponding to greater dependency. AD participants' average BI performance was 8.5 (Burns et al., 2011), 18.2 , 2017), 33.0 (Lyu et al., 2018), 52.1 (Pedrinolla et al., 2019) and 52.0 (Venturelli et al., 2012). As for comorbidities, participants were reported to suffer from a variety of diseases, most commonly bone and heart disease (Gómez Gallego and Gómez García, 2017; Pedrinolla et al., 2019; Venturelli et al., 2012; Venturelli et al., 2016).

Regarding psychosocial factors, the quality of life (QOL) was assessed in two studies and caregiver burden in three studies. Burns et al. (2011) used Blau QOL scale (Blau et al., 1977) with a score ranging from 0 to 500, with higher scores indicating greater QOL. The mean score of AD participants on the scale was 182. Santos et al. (2015) used the Quality of Life scale for patients with Alzheimer's Disease (QoL-AD; Logsdon et al., 1999), where the patient evaluates his/her own quality of life (PQoL-AD), and the caregiver/family member assesses the patient's quality of life (CQoL-

AD). The total score for both QOL-ADs ranges from 13 to 52, with higher scores indicating better QoL. The mean score of AD participants on the PQoL-AD was 34.7 and on the CQoL-AD 31.6. NPI Caregiver's Distress'scale (Cummings et al., 1994, as cited in Cummings et al., 1997) was used in two studies with mean scores of 37.4 (Lyu et al., 2018) and 7.1 (Narme et al., 2013). The score ranges between 0–60, with higher scores corresponding to greater caregiver distress. Sakamoto et al. (2013) used BEHAVE-AD Global Rating Scale (Reisberg et al., 1987, as cited in Reisberg et al., 1997) with a mean score of 1.2 at baseline. Higher scores (range: 0–4) correspond to greater caregiver distress.

As for personality, participants' personal preferences and capacities were utilized in 14 (56%) interventions (Table 1). Further, two studies extracted data from AD participants' musical and cooking abilities: Clemént et al., (2012) showed that participant's musical experience was low, and no specific cooking expertise was reported either. Narme et al. (2014) excluded participants with a high musical expertise. All interventions carried out in RCTs were delivered in long-term care sites in industrialized countries. This was also true for most of the other interventions. However, in the observational studies or analyses, the animal and plush-toy assisted interventions were delivered in the day care center (Mossello et al., 2011), the multicomponent intervention (Santos et al., 2015) in the day-hospital facility, the reminiscence therapy (van Bogaert et al., 2013) partly in the day care center, and the interventions for caregivers in the outpatient clinic (Aboulafia-Brakha et al., 2014). Two studies extracted data on the length of time lived at the facility, with an average time of 12.9 months (Pedrinolla et al., 2019) and 13.5 months (Cox et al., 2011).

Table 5 shows the number of AD participants in each AD stage and gender classes according to the beneficial, inconclusive, or harmful intervention effects on overall NPS. (See Table 2 for all the specific intervention categories, interventions, and citations.)

TABLE 5. The number of participants in each AD stage and gender classes according to the intervention effects on overall NPS

		Effects			
		Beneficial	Inconclusive	Harmful	**Total**
AD stage	Moderate	107 (22)	-	-	**107 (18)**
	Moderate to moderately severe	40 (8)		20 (18)	**60 (10)**
	Moderate to severe	139 (28)	-	81 (71)	**220 (36)**
	Severe	207 (42)	-	13 (11)	**220 (36)**
Total		**493**		**114**	**607**
Gender	Female	230 (68)	-	88 (77)	**318 (71)**
	Male	106 (32)	-	26 (23)	**132 (29)**
Total		**336**	**-**	**114**	**450**

Of the 16 beneficial interventions for overall NPS, eight involved participants with a specified stage of AD. Two recreational music therapies (Gómez Gallego and Gómez García, 2017; Lyu et al., 2018) and the reminiscence therapy (Van Bogaert et al., 2013) involved a total of 107 (22%) PWA in a moderate stage. The following five beneficial interventions involved 207 (42%) PWA in a severe stage: two recreational music therapies (Lyu et al., 2018; Sakamoto et al., 2013), two recreational relaxation therapies (Burns et al., 2011), and recreational aromatherapy (Burns et al., 2011). Of the three harmful interventions, one involved participants with a specified stage of AD: all the participants in the silent environmental intervention (Sakamoto et al., 2013) had the severe AD stage. Gender distribution was proportionally similar in beneficial and harmful interventions.

3.4. Interventions for caregivers

The only study that targeted interventions to caregivers was NRSI (Aboulafia-Brakha et al., 2014) that included 35 family caregivers semi-randomized to parallel the cognitive behavioral therapy (CBT) group and psychoeducation (EDUC) comparison group (Table 1). ANCOVA with group and time as factors revealed a significant ($p < .001$) decrease of overall NPS (BEHAVE-AD) in PWAs at the end of both interventions. The overall quality of the evidence was downgraded as moderate due to serious limitations in study design (serious RoB).

CBT was classified as therapeutic intervention, further classified as productive and interactive. The receptive and noninteractive EDUC did not contain any leisure facilitation, recreational, or therapeutic components. Both interventions aimed to help caregivers with psychosocial well-being, stress management, and coping and thus reduce NPS of cared-for PWA as well. The same therapist and author delivered both interventions using cognitive–behavioral techniques and psychoeducation in CBT –and exclusively psychoeducation in EDUC.

Both CBT and EDUC involved cared-for PWA in a moderate to severe stage of AD. At the group level, overall NPS (BEHAVE-AD) of cared-for PWA were barely observed in both groups at baseline (Table 1). The Portable Functional Assessment Questionnaire (Pfeffer et al., 1982) was used to assess ADL performance of cared-for PWA. The score ranges between 0–30, with higher scores corresponding to greater dependency. The mean score on the scale was 23 in the CBT group and 20 in the psychoeducation group. As for caregiver burden, the mean score for the Portuguese version of the Zarit Burden Interview (Zarit et al., 1980; Scazufca et al., 2002) was 35.0 in the CBT group and 31.3 in the psychoeducation group. The score ranges from 0 to 88, with higher scores indicating more burden.

4. DISCUSSION

The aim of this systematic review was to examine the range and effects of recent non-pharmacological interventions on NPS in moderate to severe stages of AD. As a secondary objective, the characteristics of interventions and participants and the interactions between them was described.

4.1. The range and effects of interventions

The included 14 studies involved both psychosocial and environmental interventions. According to the American Psychiatric Association (APA; Rabins et al., 2007; Rabins et al., 2017) practice guidelines, the psychosocial interventions for PWA were further divided into stimulation-oriented (music, exercise, relaxation, aromatherapy, animal- and plush toy assisted activity), behavior-oriented (cooking), emotion-oriented (reminiscence, lyrics reading), cognition-oriented (reality orientation), and stimulation- and cognition-oriented interventions (exercise and cognitive training, multimodal stimulation). Interventions were targeted at caregivers in only one study involving two interventions: the cognitive behavioral therapy and the psychoeducation (Aboulafia-Brakha et al., 2014).

All nonpharmacological orientations, except cognitive ones, are recommended with a moderate confidence for NPS in AD (APA; Rabins et al., 2007; Rabins et al., 2017). As for the moderate to severe stages of AD, the findings of this review support the recommendation. Based on the direction of the high-quality effects of interventions carried out in RCTs, the nonpharmacological interventions had significant beneficial effect on overall NPS. The significant beneficial, but less confidential effects, were found in agitation and anxiety as well.

The evidence from this review was statistically sufficient to support stimulation-oriented interventions in treating overall NPS. Carried out in Venturelli et al. (2016) RCT, the only cognitive-oriented intervention in this review was exclusively cognitive therapy in nature and classified as harmful. According to Fukushima et al. (2016), cognitively-oriented stimulation is effective in

treating depression, apathy, and anxiety in AD. In line with this, the multimodal stimulation interventions carried out in Venturelli et al. (2016) RCT and Santos et al. (2015) NRCT were beneficial for NPS. Both the CBT and psychoeducation for caregivers in Aboulafia-Brakha et al. (2014) NRSI was significantly beneficial for PWA suffering overall NPS.

Strong evidence supports the use of certain environmental interventions, especially multisensory environments, in decreasing agitation and anxiety in PWA (Jensen et al., 2017). Indeed, the multisensory therapeutic garden (Pedrinolla et al., 2019) for overall NPS was the most effective intervention carried out in all RCTs included in this review. Conversely, the deterioration of NPS reached significance in most of the NPI subdomains in a silent, standard room environment with a provider (Sakamoto et al., 2013). The results are consistent with the theory of the Progressively Lowered Stress Threshold model (PLST; Hall & Buckwalter, 1987), which proposes that dysfunctional behaviors occurring later in the day are caused by an exceeded stress threshold due to disordered person-environment interaction.

Olazarán et al. (2010) found support in their review for each intervention orientation in the treatment of NPS in mild cognitive impairment and mild to severe AD. They concluded that nonpharmacological interventions are effective for this purpose and generally have no side effects. However, the adverse events were reported in this review in five studies, two of which reported agitation (Burns et al., 2011), anxiety, and discomfort (Venturelli et al., 2016) during the interventions. Thus, the likelihood of adverse events may increase as the disease progresses.

4.2 The characteristics of interventions and participants

In general, the results of this review were in line with the evidence-based idea of the Comprehensive Process Model of Engagement (CPME; Cohen-Mansfield et al., 2009) in that exposure to an appropriately engaging external stimulation, particularly social, or a lack of it can have dramatic positive or negative behavioral effects through a change in affect in PWA. According to the model, the engagement with a stimulus is affected by the interplay between the characteristics of environment, person, and stimulus.

The combination of psychosocial intervention characteristics may play a role in their effectiveness. Most of the interventions were stimulation-oriented and recreational therapies in nature. In general, the recreational therapy approach is a strongly evidence-based practice in the biopsychosocial domains of health, wellness, and quality of life (Austin et al., 2020). In line with this, all the recreational interventions included in the review were beneficial for overall NPS in moderate to severe AD. There were only slightly more productive interventions than receptive ones, so PWA seem to benefit from both productive and receptive interventions. Furthermore, most of the

interventions were interactive. Since there were also three participatory interventions (Burns et al., 2011) and one noninteractive (Sakamoto et al., 2013) intervention, admittedly less beneficial ones, interactivity does not appear to be an absolute prerequisite for clinically beneficial interventions for NPS in moderate to severe AD.

Since therapeutic interventions involve more demanding and specialized goals, they also require more focused concentration from participants than leisure facilitation and recreational interventions. In this review, the two therapeutic interventions were the harmful, productive, cognitive-oriented reality orientation therapy (Venturelli et al., 2016) and the beneficial, productive, emotion-oriented reminiscence therapy (Van Bogaert et al., 2013). Thus, the therapeutic nature of intervention can be harmful for NPS in moderate to severe AD if its orientation is primarily cognitive.

The baseline factors that are associated with the frequency and severity of NPS (Robert et al., 2005; Nagata et al., 2017) were not adequately assessed in most of the studies. Here, the association of important factors with the effects of interventions on overall NPS were explored; these associated factors were demographic (gender, age), biological (antipsychotic drugs), clinical (NPS, AD stage, ADL-performance), and psychosocial (QOL, personal preferences, caregiver stress).

The baseline NPS were presence at the group level in all the studies assessing the intervention effects on overall NPS. The intervention effects did not vary according to the gender, age, and tailoring by the personal preferences of the PWA, the proportion of PWA taking antipsychotic drugs (Gómez Gallego & Gómez García, 2017; Pedrinolla et al., 2019; Venturelli et al., 2016), the quality of life (QOL; Burns et al., 2011), ADL-performance (Burns et al., 2011; Gómez Gallego & Gómez García, 2017; Lyu et al., 2018; Pedrinolla et al., 2019; Venturelli et al. 2012), and the level of caregiver distress (Lyu et al., 2018; Narme et al., 2013; Sakamoto et al. 2013). All high-quality evidence was obtained from RCTs, which were all carried out in long-term care sites.

The effective interventions in a moderate AD stage were recreational and stimulation-oriented music therapies (Gallego and Garcia, 2017; Lyu et al., 2018) and the therapeutic emotion-oriented reminiscence (Van Bogaert et al., 2013). Indeed, some forms of cognitions, especially social (Evans-Roberts & Turnbull, 2010; Halteren-van Tilborg et al., 2007; Gillioz et al., 2009) and musical (Jacobsen et al, 2015), are relatively well preserved in moderate to severe AD, while praxis, orientation, memory, and language continue to impair in PWA entering the severe stage of AD (Gillioz et al., 2009). In line with this, all the interventions for PWA with severe AD were recreational therapies and leisure facilitation interventions involving the significantly beneficial music interventions (Lyu et al., 2018; Sakamoto et al., 2013), clinically beneficial relaxation (Burns et al., 2011), and aromatherapy (Burns et al., 2011). In terms of the AD stage, no differences were found in the distribution of the harmful interventions (Pedrinolla et al., 2019; Sakamoto et al. 2013; Venturelli et al., 2016).

Millán-Calenti et al. (2016) concluded that music therapy, especially when group-based and individualized, is an ideal intervention for PWA with agitation, but the effects are not long-term. This review showed that it may be possible to modify the impact of intervention characteristics and complex intervention pathways on outcomes in ways to implement the intervention. All the seven stimulation-oriented music interventions (Clement et al., 2012; Cox et al., 2011; Gallego & Garcia, 2017; Lyu et al., 2018; Narme et al., 2014; Sakamoto et al., 2013) and two behavior-oriented cooking interventions (Clement et al., 2012; Narme et al., 2014) were beneficial for NPS assessed at the end of the interventions. The beneficial effects of group-based music interventions were still significant at four weeks (Clement et al., 2012; Narme et al., 2014) and even at three months (Lyu et al., 2018) after the interventions and the tailored cooking intervention (Narme et al., 2014) at four weeks after the intervention. By contrast, in individually delivered and tailored music interventions (Sakamoto et al., 2013) the beneficial effects had been lost after the three-week follow-up. In this study, the long-term effects after the interventions were assessed only in the four studies above.

4.3. Review and study limitations

This systematic review identified peer-reviewed, English articles from the three most relevant databases as well as through comprehensive forward and backward reference searches involving all the identified articles and reviews on the topic. Despite a comprehensive search, non-English, locally published and unpublished articles may have been missed. Because the primary aim of this study was to explore the range and effects of nonpharmacological interventions for NPS in moderate to severe AD, the broad definition of inclusion criteria for the interventions, comparison interventions, outcomes and the study designs was warranted. However, this meant that low-quality NRSIs were included as well. Choosing the narrow population criteria was an expedient choice, because the AD stage is expected to affect the range of interventions and modify their effects. The conclusions that can be drawn from the synthesis method of vote counting based on direction of effect addresses any evidence of an effect rather than the average or statistically significant intervention effect. However, any evidence of an effect can be important when studying the effects of interventions on NPS in advanced AD. Based on the high-quality evidence that only answered the review questions, the results were generalizable to the primary outcome of this review (overall NPS at the end of the intervention) and intended population dwelling in long-term care sites in industrialized countries.

Certain limitations existed in relation to how the studies included were conducted and reported. The overall risk of bias (RoB) of three RCTs (Pedrinolla et al., 2019; Venturelli et al., 2016; Jihui et al., 2018) was classified as having some concerns of risk. The RoB of all other studies was at least high or severe and in three observational studies (Cox et al., 2011; Gómez Gallego & Gómez

García, 2017; Santos et al., 2015), it was critical. However, the quality of evidence (GRADE; Schunemann et al., 2013) regarding overall NPS obtained from RCTs was graded as high, because the limitations of these studies did not apply to the most important aspects of the domains of RoB. Furthermore, the quality of evidence obtained from RCTs was not downgraded by other characteristics of evidence (consistency, directness, precision, publication bias). By contrast, the quality of evidence obtained from NRSIs/others was graded as very low because of serious limitations in the study designs and imprecision. The overall quality of the evidence obtained from the interventions targeted to caregivers (Aboulafia-Brakha 2014) was downgraded as moderate due to serious RoB.

Describing both interventions and their implementation were incomplete, particularly in relation to deliverer and participant adherence, adverse events, and co-interventions. Regarding the baseline characteristics of participants, the reporting of most important factors affecting NPS was inadequate; these factors were demographic (ethnicity, education), clinical (social cognitive performance, ADL-performance, history of / present disturbing health conditions), and psychosocial (QOL, personality, skill level, time since admission to the facility, caregiver burden).

4.4. Implications for research and practice

This review has described the range and effects of nonpharmacological interventions for NPS in moderate to severe AD. The evidence was sufficient to conclude that interventions were beneficial in treating overall NPS, agitation, and anxiety. As for other NPS domains, more research is needed. The low number of nonpharmacological interventions for PWA in relation to the prevalence and severity of AD indicates that all kinds of research designs carried out in different contexts are needed in intervention development. More research is needed regarding the orientations (stimulation, emotion, behavior, cognitive) and the leisure facilitation and therapeutic interventions. The effects of intervention characteristics, complex pathways, and implementation on outcomes should be investigated further in the future. Moreover, the paucity of interventions aimed at caregivers of persons suffering from moderate to severe AD and related NPS was striking considering that the caregiver burden and NPS both trigger and exacerbate each other, and the nonpharmacological interventions have the potential to reduce both (Isik et al., 2019).

In this review, PWA with moderate to severe AD and related NPS generally show high positive engagement in nonpharmacological interventions and benefit from them. At the same time, they may also be more susceptible to harmful effects and adverse events of these interventions than PWA with mild AD, which should be clarified in the future. The specific trajectory of decline in AD in social and cognitive performance and in ADL should be considered in the intervention

development. In this review, the relative preservation of social and musical cognition may have explained the beneficial impact of interactive and musical interventions even at a moderate and severe stage of AD.

As the formal recommendations state (Geda et al., 2013; Kales, Gitlin, & Lyketsos, 2014; Lyketsos et al., 2006, Robins et al., 2017; Volicer, 2018), careful assessment of NPS and their causes should be conducted before selecting the most appropriate nonpharmacological intervention with the strongest evidence base. According to this review, the intervention goals, techniques, and theories of mechanisms of action should also be considered in relation to the intervention recipient's characteristics, needs, and preferences when selecting and implementing the intervention.

4.5. Conclusions

Little research exists on nonpharmacological interventions for NPS in moderate to severe AD. This is especially true for research into interventions aimed at caregivers of PWA at the moderate to severe stage. In this review, the high-quality evidence base was obtained for treating overall NPS with recreational therapies involving stimulation-oriented and enjoyable activities with the aim of self-actualization, wellness, and quality of life. The problem is that the evidence of their beneficial effects is generalizable only to the long-term care environment in industrialized countries.

As a growing majority of all PWA live at home in low- and middle-income countries, more development of nonpharmacological interventions is needed to meet these PWA's particular needs, which means that more attention must be paid to caregivers throughout the world. Furthermore, in order to design, target, and implement the nonpharmacological interventions optimally, the clearest possible understanding of nonpharmacological intervention complexity is needed. The effective, ineffective, and harmful intervention components and important mediators and moderators of effect can be identified in complex interventions for NPS in moderate to severe AD, as long as research is conducted and reported adequately.

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APPENDICES

Appendix A. Data collection form: Study and intervention characteristics

1. STUDY IDENTIFICATION AND METHODS

Type ”NR” for not reported, and ”NA” for not applicable (not measured etc.). Prefer direct quotation (copy and paste) with quotation marks when specifying.

STUDY AND REPORT IDENTIFICATION

1.1. Name of data extractor and date of data extraction completed

1.2. Study ID

Code: S1. (consecutive numbering), surname of first author and year first full report of study was published/appearanced

1.3. Report ID

Code: R1. (consecutive numbering), surname of first author and year of publication/appearance (e.g. R1. Smith 2018)

1.4. Article

1.5. Type of study

If journal article, specify the name and the issue of the journal

1.6. Peer-reviewed

a) Yes	b) No	c) Not reported

Please enter your comment here:

1.7. Organization

1.8. Ethical approval obtained

a) Yes	b) No	c) Not reported

Please enter your comment here:

1.9. Registered

a) Registered prospectively	b) Registered retrospectively	c) Registered	d) Not registered	e) Not reported

Please enter your comment here:

1.10. Protocol

a) Yes, specify	b) No	c) Not reported

Please enter your comment here:

1.11. Completed and published

a) Completed:	b) Accepted:	c) Published:

AIM OF STUDY

1.12. Descriptions and hypotheses as stated in report/paper

1.13. Participant-relevant primary outcome domains and assessment methods

1.14. Participant-relevant secondary outcome domains and assessment methods

STUDY METHODS

1.15. Randomized design is

a) Parallel-group design, specify	b) Cluster-randomized design, specify	c) Crossover design, specify	d) Other, specify

Please enter your comment here:

1.16. Unit of analysis

1.17. A sample size calculation performed a priori

a) Yes, specify	b) No

Please enter your comment here:

1.18. Eligible outcomes

a) Primary outcome I	b) Primary outcome II	c) Secondary outcome I	d) Secondary outcome II	e) Secondary outcome III

1.19. Enrolment start and end dates

a) Start date	b) End date

1.20. Recruitment and sampling procedures used

1.21. Single or multicentre study (number of recruiting centres)

a) Single	b) Multicenter; number of recruiting centres	c) Other, specify

Please enter your comment here:

1.22. Recruitment settings I

a) Country:	b) Town/Region:

1.23. Recruitment settings II

Specify only when you choose an answer.

a) University	b) Research/rehabilitation centre	c) Hospital	d) Assisted-living facilities:	e) Day care site attended:	f) Other:

1.24. Randomization: was the allocation sequence random?

a) Yes	b) Probably yes	c) Probably no	d) No

Please enter your comment here:

1.25. Concealment: was the allocation sequence concealed until participants were assigned to interventions?

a) Yes	b) Probably yes	c) Probably no	d) No

Please enter your comment here:

1.26. Blindning I: were participants aware of their assigned intervention during the trial?
Choose one of the following answers

a) Yes	b) Probably yes	c) Probably no	d) No

Please enter your comment here:

1.27. Blindning II: were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

a) Yes	b) Probably yes	c) Probably no	d) No

Please enter your comment here:

1.28. Randomized studies: specific study design features of randomized study: risk of bias

a) randomization process	b) deviations from the intended interventions	c) missing outcome data	d) measurement of the outcome	e) selection of the reported results:	f) Overall	g) Others

1.29. Non-randomized study design is
Comment only when you choose an answer.

Non-randomized experimental study (e.g. quasi-randomized and non-randomized controlled trials):	Observational study (e.g. before-after):	Other:

1.30. Non-randomized studies: how were groups of individuals or clusters formed by?

1.31. Non-randomized studies: specific study design features of non-randomized studies

a) confounding	b) selection of participants into the study	c) classification of interventions	d) deviations from intended interventions	e) missing data:	f) measurement of outcomes:	g) selection of the reported result:

h) Overall bias:
i) Others:

1.32. Study arms

Name all study arms shortly.

a) Study arm1	b) Study arm 2	c) Study arm 3	d) Study arm 4

1.33. Length of participant follow-up

a) Time point I	b) Time point II	c) Time point III	d) Follow-up I	e) Follow-up II	f) More

1.34. Funding sources; was source(s) of monetary or material support for research reported in report?

a) Yes, specify	b) No

Please enter your comment here:

1.35. Possible conflicts of interests for study authors reported

a) Yes, specify	b) No

Please enter your comment here:

Specify the study methods freely

2. PARTICIPANTS

Study eligibility criteria & characteristics of participants at the beginning of the study

Type ”NR” for not reported, and ”NA” for not applicable (not measured etc.). Prefer direct quotation (copy and paste) with quotation marks when specifying.

STUDY ELIGIBILITY CRITERIA

2.1. AD diagnosis: were eligibility criteria reported regarding the diagnosis of probable or possible Alzheimer's disease?

a) Yes, specify	b) No

Please enter your comment here:

2.2. AD stages: were eligibility criteria reported regarding the specific stage(s) of Alzheimer's disease?

a) Yes, define the stages	b) No

Please enter your comment here:

2.3. Neuropsychiatric symptoms: were eligibility criteria reported regarding neuropsychiatric symptoms?

a) Yes, define the symptoms	b) No

Please enter your comment here:

2.4. Cognitive performance: were eligibility criteria reported regarding the general or social cognitive performance?

a) Yes, specify	b) No

Please enter your comment here:

2.5. Activities of daily living: were eligibility criteria reported regarding the activities of daily living performance?

a) Yes, specify	b) No

Please enter your comment here

2.6. Disturbing conditions: were eligibility criteria reported regarding participants (patients) experiencing conditions which may disturb assessments or interventions?

a) Yes, specify	b) No

Please enter your comment here:

2.7. History of disturbing conditions: were eligibility criteria reported regarding participants having a history of conditions which may disturb assessments or interventions?

a) Yes, specify	b) No

Please enter your comment here:

2.8. Co-interventions: were eligibility criteria reported regarding any separate non-pharmacological co-interventions?

a) Yes, specify	b) No

Please enter your comment here:

2.9. Medication: were eligibility criteria reported regarding medication?

a) Yes, specify	b) No

Please enter your comment here:

2.10. Residential environment: were eligibility criteria reported regarding the residential environment of the participants?

a) Yes, specify	b) No

Please enter your comment here:

2.11. Skill level: were eligibility criteria reported regarding the skill level/experience of the participants?

a) Yes, specify	b) No

Please enter your comment here:

2.12. Age: were eligibility criteria reported regardind age?

a) Yes, specify	b) No

Please enter your comment here:

2.13. Other criteria: Were any other eligibility criteria reported not mentioned above?

a) Yes, specify	b) No

Please enter your comment here:

2.14. Specify eligibility criteria freely

BASELINE CHARACTERISTICS OF PARTICIPANTS

2.15. Consent: information about obtaining a concent reported?

a) Yes, specify	b) No

Please enter your comment here:

2.16. Diagnosis of Alzheimer's disease

Comment only when you choose an answer.

a) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)	
b) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)	
c) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)	
d) National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)	
e) Magnetic resonance imaging (MRI)	
f) Positron emission tomography (PET)	
g) Proteins in cerebrospinal fluid (CSF)	
h) Other, specify	

2.17. Total number of study groups:

2.18–2.19. Eligible study groups & baseline imbalances					
Characteristics	1. Study group, n	2. Study group, n	3. Study group, n	4. Study group, n	5. Entire study, n
2.18. Eligible study groups, n randomized	a)	b)	c)	d)	e)
2.19. Reported baseline imbalances					
2.20–2.35. AD stage/severity I & AD stage/severity II					
Characteristics	1. Study group	2. Study group	3. Study group	4. Study group	5. Entire study
2.20. Measurement tool I	a)	b)	c)	d)	e)
2.21. n					
2.22. Mean					
2.23. SD					
2.24. Median					
2.25. Range					
2.26. Stage					
2.27. Others					
2.36.–2.42. Activities of daily living performance					
2.36. Measurement tool	a)	b)	c)	d)	e)
2.37. n					
2.38. Mean					
2.39. SD					
2.40. Median					
2.41. Range					
2.42. Others					

2.43.–2.49. General cognitive performance					
2.43. Measurement tool	a)	b)	c)	d)	e)
2.44. n					
2.45. Mean					
2.46. SD					
2.47. Median					
2.48. Range					
2.49. Others					
2.50.–2.56. Social cognitive performance					
2.50. Measurement tool	a)	b)	c)	d)	e)
2.51. n					
2.52. Mean					
2.53. SD					
2.54. Median					
2.55. Range					
2.56. Others					
2.57.–2.63. Quality of life i.e. quality of life, social support, quality of care or unmet needs					
2.57. Measurement tool	a)	b)	c)	d)	e)
2.58. n					
2.59. Mean					
2.60. SD					
2.61. Median					
2.62. Range					
2.63. Others					
2.64.–2.70. General neuropsychiatric symptoms					
2.64. Measurement tool	a)	b)	c)	d)	e)
2.65. n					
2.66. Mean					
2.67. SD					
2.68. Median					
2.69. Range					
2.70. Others					
2.71.–2.161. Specific neuropsychiatric symptoms					
2.71. Measurement tool I	a)	b)	c)	d)	e)
2.72. n					
2.73. Mean					
2.74. SD					
2.75. Median					
2.76. Range					
2.77. Others					
2.162.–2.169. Comorbid conditions					

2.162. Chronic somatic diseases or impairments I(n/%)	a)	b)	c)	d)	e)
2.163. Chronic somatic diseases or impairments II (n/%)					
2.164. Chronic somatic diseases or impairments III (n/%)					
2.165. Chronic somatic diseases or impairments IV (n/%)					
2.166. Chronic mental disorders I (n/%)					
2.167. Chronic mental disorders II (n/%)					
2.168. Chronic mental disorders III (n/%)					
2.169. Others					
2.170.–1.77. Medication					
2.170. Antidementia drug I (n/%)	a)	b)	c)	d)	e)
2.171. Antidementia drug II (n/%)					
2.172. Antidementia drug III (n/%)					
2.173. Psychopharmaceutical drug I (n/%)					
2.174. Psychopharmaceutical drug II (n/%)					
2.175. Psychopharmaceutical drug III (n/%)					
2.176. Analgesics					
2.177. Others					
2.178.–2.189. Sociodemographics					
2.178. Ethnicity (n/%)	a)	b)	c)	d)	e)
2.179. Ethnicity (n/%)					

2.180. Ethnicity (n/%)					
2.181. Male (n/%)					
2.182. Female (n/%)					
2.183. Age: mean					
2.184. Age: SD					
2.185. Age: range					
2.186. Age at onset of and/or duration of AD					
2.187. Marital status					
2.188. Education					
2.188. Skill level (skill, level)					
2.189. Others					
2.190.–193. Physical and social environment Residence type, facility & time since admission to the facility, life events etc.					
2.190. Residence type	a)	b)	c)	d)	e)
2.191. Facility & time since admission to the facility					
2.192. Life events					
2.193. Others					
2.194.–2.200. Caregiver burden					
2.194. Measurement tool	a)	b)	c)	d)	e)
2.195. n					
2.196. Mean					
2.197. SD					
2.198. Median					
2.199. Range					
2.200. Others					
2.201.-2.203. Personality: different assessment methods, personality style of interest, experience, expertise, preferences, hobbies, etc.					
2.201. Premorbid personality	a)	b)	c)	d)	e)
2.202. Current personality					
2.203. Others					
2.204. Specify baseline characteristics of participants freely					
	a)	b)	c)	d)	e)

3. INTERVENTIONS, SETTINGS AND CONTEXTS

Type ”NR” for not reported, and ”NA” for not applicable (not measured etc.). Prefer direct quotation (copy and paste) with quotation marks when specifying.

PRELIMINARY INFORMATION

3.1. Existing intervention protocol

a) Yes, specify	b) No	c) Not reported

Please enter your comment here:

3.2. Whose behaviour/action the intervention intended to change (where applicable)?

a) Individual with AD	b) Caregiver, specify	c) Others, specify

Please enter your comment here:

3.3. Co-interventions

Non-pharmacological co-interventions, specify:
Medications, specify:

ESSENTIAL INTERVENTION COMPONENTS

3.4.–3.7. Essential procedures, activities, or processes to the intervention and the comparison

	Different procedures in relation to comparisons	Different/same	Different/same	Same	Same	Others
1. The procedures essential to the intervention I:	a)	b)	c)	d)	e)	f)
2. The procedures essential to the intervention II:						
3. The procedures essential to the comparison I:						
4. The procedures essential to the						

comparison II:						

3.8. Detailed descriptions for the essential procedures, activities, and/or processes

a) Procedure 1:
b) Procedure 2:
c) Procedure 3:
d) Procedure 4:
e) Procedure 5:
f) Procedure 6:
g) Others:

THE TIDieR CHECKLIST: INTERVENTIONS

3.9. Brief name
Provide the name or a phrase that describes the intervention:

3.10. Why
The rationale, theory, or goal behind an important element of an intervention:

3.11. What: materials
a) Physical/informational materials provided to participants, accessed:
b) Physical/informational materials used in intervention delivery, accessed:
c) Physical/informational materials used in training of intervention providers, accessed:
d) Others, accessed:

3.12. Who provided I
a) Intervention provider and the number of providers:
b) Expertise:
c) Background
d) Others:

3.13. Who provided II

a) Pre-existing specific skills, expertise, and experience required:

a) yes	b) no	c) NR

b) Any specific training given:

a) yes	b) no	c) NR

c) Competence in delivering the intervention assessed before / throughout the study:

a) yes	b) no	c) NR

d) Providers were doing the intervention as part of their normal role:

a) yes	b) no	c) NR

e) Providers were were specially recruited as providers for purposes of the study:

a) yes	b) no	c) NR

f) Providers were reimbursed for their time or provided with other incentives (if so, what) to deliver the intervention as part of the study:

a) yes	b) no	c) NR

g) Others:

3.14. How I
Comment only when you choose an answer.

a) to one participant at a time	b) to a group of participants, group size:	c) delivered face to face	d) delivered by distance	e) delivered by a combination of modes	f) interactive	g) not interactive	h) Others

3.15. How II
Other delivery features considered essential or likely to influence outcome:

3.16. Where I
Country & Town/Region:

3.17. Where II
Specify the features or circumstances about the location.

a) Long term hospital	b) Long term care site	c) Research/rehabilitation centre	d) Assisted-living facilities	e) Day care site attended	f) Outpatient clinic	g) Home dwelling site	h) Others

3.18. When and how much

a) The number of times the intervention was intended to deliver, fixed?
b) Over what intended period of time, fixed?
c) Intended schedule of sessions, fixed?
d) Intended duration of sessions, fixed?
e) Intended intensity of sessions, fixed?
f) Timing of the intervention (in relation to relevant events)?

3.19. Tailoring

a) Any variables/constructs used for participant assessment before tailoring?
b) Tailored to individuals or groups of individuals?
c) What is tailored?
d) Why?
e) When?
f) How?

3.20. Modifications

a) What was modified?
b) Why?
c) When modifications occurred?
d) How the modified intervention differed from the original?
e) Others

3.21. How well 1: planning

The types of measures used to determine intervention fidelity:
a) Training of intervention providers
b) Delivery of the intervention
c) Receipt of the intervention
d) Others

3.22. How well 2

Strategies and tools used to maintain or improve fidelity before delivery of the intervention or during the study

a) Training of intervention providers: strategies and tools used to maintain or improve fidelity before delivery of the intervention or during the study
b) Delivery of the intervention
c) Receipt of the intervention; strategies and tools used to maintain or improve fidelity before delivery of the intervention or during the study
d) Others

3.23. How well 3

If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.

a) Training of intervention providers; the extent to which the intervention was delivered as planned:
b) Delivery of the intervention; the extent to which the intervention was delivered as planned:
c) Receipt of the intervention; the extent to which the intervention was delivered as planned:
d) Others:

3.24.–3.91. THE TIDieR CHECKLIST: THE COMPARISON I–III

3.92. Specify interventions, settings and contexts freely

4. OUTCOMES & ADVERSE EVENTS

OUTCOMES

Type ”NR” for not reported, and ”NA” for not applicable (not measured etc.). Prefer direct quotation (copy and paste) with quotation marks when specifying.

4.1. Outcome domain or title (e.g. anxiety)

4.1.1. Eligibility criteria regarding outcome domain

a) Yes, specify	b) No

Please enter your comment here:

4.1.2. Measurement tool or instrument & definition of clinical outcomes or endpoints

4.1.3. Upper and lower limits, and whether a high or low score is favourable, definitions of any thresholds if appropriate

4.1.4. Specific metric used to characterize each participant’s results

4.1.5. Method of aggregation

4.1.6. Timing of outcome measurements

4.2.–4.4. Outcome domain or title (e.g. anxiety)

ADVERSE EVENTS

4.5. Adverse events or effects collected

4.5.1. Systematically, specify (i.e. any coding system or standard medical terminology used):

4.5.2. Non-systematically, specify:

4.5.3. Systematically and non-systematically, specify:

4.5.4. Not collected, specify:

4.5.5. Not reported:

4.6. Adverse events; definition(s) or name(s) of the adverse events (e.g. dizziness):

4.7. Adverse events; reported and categorized intensity of the adverse event:

4.8. Adverse events: relatedness: the trial investigators identified the adverse event as being related to the intervention:

4.9. Adverse events: time point:

4.10. Adverse events; selection for inclusion: any reported methods for how adverse events were selected for inclusion in the publication

4.11. Adverse events; associated results:

4.12. Adverse events; specify freely

5. RESULTS AND EVIDENCE FOR GRADE

Type ”NR” for not reported. Prefer direct quotation (copy and paste) with quotation marks when specifying.

5.1. Outcome domain, measurement tool or instrument, the type of instrument scores (e.g. ranging from 0 to 100):

5.2. Evidence/data for GRADE

Study limitations, inconsistency of results, imprecision and publication bias:

Type relevant study group(s), time point, summary data (n), the point estimates, precision and significance, risk of bias at each time point for each study arm.

Result: the combination of a point estimate (such as a mean difference or risk ratio) and a measure of its precision (such as a confidence interval) for a particular study outcome.

	Study arm 1	Study arm 2	Study arm 3	Study arm 4	Between-group estimates
5.2.1. a–e) Randomly assigned					
5.2.2. a–e) Baseline					
5.2.3. a–e) Time point 1					
5.2.4. a–e) Time point 2					
5.2.5. a–e) Time point 3					
5.2.6. a–e) Follow-up 1					
5.2.7. a–e) Follow-up 2					

5.3. Indirectness of evidence:
Type descriptions for populations (applicability), interventions (applicability), outcome measures (surrogate outcomes) and comparisons (regarding GRADE).

5.3.1. Populations: applicability

5.3.2. Interventions: applicability

5.3.3. Outcome measures: surrogate outcomes
5.3.4. Comparisons: regarding GRADE

5.4. Key conclusions of study authors

Appendix B. Risk of bias for randomized controlled trials

Author year	1. Randomization	2. Deviations from the intended interventions	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	6. Overall
Burns 2011	Low	High	High	Low	Some concerns	High
Clemént 2012	Some concerns	Some concerns	High	High	Some concerns	High
Jihui 2018	Low	Low	Low	Low	Some concerns	Some concerns
Narme 2014	Some concerns	Some concerns	High	Low	Some concerns	High
Pedrinolla 2019	Low	Low	Some	Low	Low	Some concerns
Sakamoto 2013	Low	Low	Low	Low	Some concerns	Some concerns
Venturelli 2016	Some	Low	Low	Low	Some concerns	Some concerns

Appendix C. Risk of bias for observational studies

First author year	Con-founding	Selection of participants into the study	Classi-fication of inter-ventions	Deviations from intended interventions	Missing data	Measure-ment of outcomes	Selection of the reported result	Overall
Aboulafia-Brakha 2014	Serious	Low	Low	Moderate	Low	Serious	Moderate	Serious
Cox 2011	Critical	Low	Low	Serious	Low	Serious	Moderate	Critical
Gallego 2017	Critical	Low	Low	Low	No information	Low	Moderate	Critical
Mossello 2011	Serious	Low	Low	Low	No information	Serious	Moderate	Serious
Santos 2015	Critical	Low	Low	Low	Low	Serious	Moderate	Critical
Van Bogaert 2013	Serious	Serious	Low	Low	Low	Serious	Moderate	Serious
Venturelli 2012	Serious	Serious	Low	Low	Low	Serious	Moderate	Serious

Appendix D. Certainty of the evidence

Design: number of studies	Number of interventions (paricipants)	Number of target interventions (participants)	Number of comparison interventions (participants)	Assessment methods	Effect	Limitations in study designs	Inconsistency of results	Indirectness of evidence	Other modifying factors	Overall quality
All	**19 (646)**	**9 (238)**	**13 (408)**		**16/19****	**No serious**	**No important**	**Direct**	**None**	**High**
RCTs: 6		6	12							
Beneficial	Therapeutic garden	1 (82)	-	**NPI*****	1/1	No serious				
	Exercise	1 (20)	-	**NPI***	1/1	No serious				
	Exercise and cognitive training	-	1 (20)	**NPI***	1/1	No serious				
	Lyrics reading	-	1 (68)	NPI[a]	1/1	No serious				
	Music	3 (98)	1 (67) 2 (26) 1 (18)	NPI[a] BEHAVE-AD **NPI***	3/3	No serious No serious Serious				
	Relaxation	-	2 (76)	NPI[a]	2/2	Serious				
	Aromatherapy	1 (38)	-	NPI[a]	1/1	Serious				
	Cooking	-	1 (19)	**NPI****	1/1	Serious				
Inconclusive	Cognitive training	-	1 (20)	NPI	0/1	No serious				
Harmful	Silent environment		1 (13)	NPI	-0/1	No serious				
	Standard environment		1 (81)	NPI	-0/1	No serious				
NRSIs/others: 3	**4 (49)**	**3 (49)**	**1 (10)**		**4/4**	**Serious**	**No important**	**Direct**	**Imprecise**	**Very low**
Beneficial	Music	1 (17)	-	NPI***	1/1	Very serious				
	Reminiscence	1 (22)	-	NPI	1/1	Serious				
	Animal	1 (10)	-	NPI	1/1	Serious				
	Plush-toy	-	1 (10)	NPI	1/1	Serious				

* = p < .05, ** = p < .01, *** = p < .001