Recent findings on nonpharmacological therapies in Alzheimer's Disease: New hope for patients?

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ABSTRACT

Worldwide, nearly 44 million people have Alzheimer's disease (AD) or related dementia (Alzheimer statistics 2016). This number is expected to triple during the coming 35 years (Prince et al, 2016). AD has a progressive character and is associated with cognitive decline and several neuropsychological disturbances like agitation, anxiety and depression. Quality of life (QoL) decreases in AD. The medication that is currently available is symptomatic and is limited to delaying the progression of symptoms with several months (Qaseem et al., 2008) Nonpharmacological interventions are being studied intensively and evidence for the effectiveness of these therapies is growing. Several different nonpharmacological therapies have been proposed to reduce cognitive, psychosocial and behavioural alterations in AD patients, but also to improve motor impairment, quality of life and so on (Gallego, 2017). The aim of this study is to describe the most recent studies that have investigated such a nonpharmacological therapy. Although some of the studies showed promising results, further research will be necessary to validate these results. Validations are necessary considering some studies did not include a control group and most studies had small sample sizes and were conducted in a short time interval. Furthermore, more attention must be paid to potential mechanisms of action and brain areas involved in certain therapies. Even though nonpharmacological therapies seem promising in improving QoL, cognition, motor-skills, awareness etc. it should be mentioned that it might be difficult to improve everyday functioning in AD patients.

Introduction

AD is a common neurogenerative disease (Apostolova, 2016) and the most prevalent form of age-related dementia. AD was already one of top 50 global causes of years of life lost in 2013 (GBD, 2013). With age being the greatest risk factor for AD (Apostolova, 2016) and the rising global age expectancy, the mortality rate will increase much further. It is expected that in 2030 AD will be the seventh highest cause of death in high-income countries (Mathers et al., 2006).

Cognitive decline and neuropsychiatric disturbances are the major symptoms of AD. Memory decline is considered the leading symptom. In early stages of the disease, memory decline remains limited to the episodic memory. At first, only new episodic memories are affected, but in later stages, all episodic memories become impaired. Eventually, also working memory and semantic memory become affected, (Apostolova, 2015) (Figure 1).

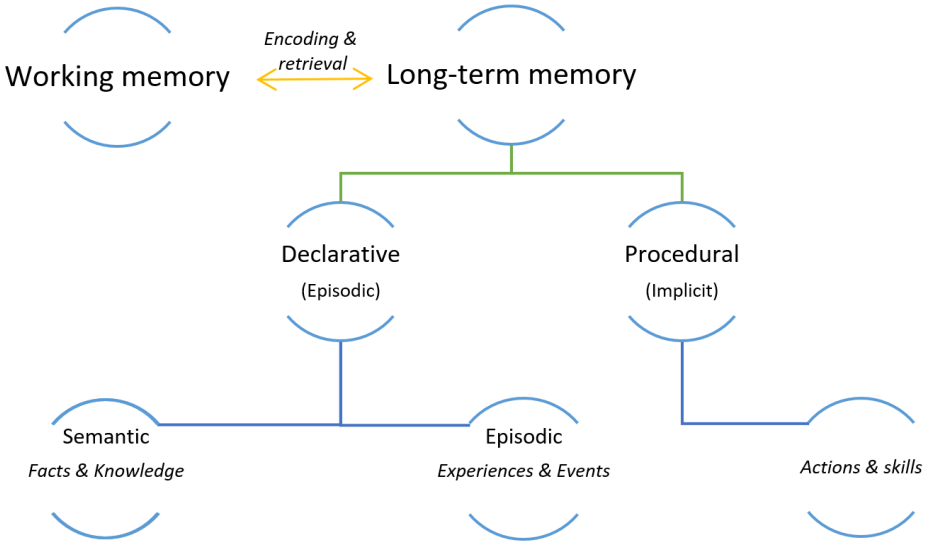

Figure 1: Schematic overview of working memory and long-term memory (Sprenger, 1999)

Other forms of cognitive decline which are often seen in early stages of AD are: mild language disturbance, executive dysfunction and decline in visuospatial skills. Several neuropsychiatric disturbances are associated with AD. In early stages apathy, anxiety, irritability and depressive symptoms are often found. As the disease progresses appetite, sleep, disinhibition, perception and thought become disturbed. This disruption of perception and though causes hallucinations and delusions. In the later stages of the disease, reflexes will be affected. In the end stages, patients are bedridden, mute and incontinent (Apostolova, 2016) (Figure 2).

AD is characterized by a loss of cholinergic neurons, mainly in the nucleus basalis of Meynert (Whitehouse et al., 1982), which results in a reduced activity of choline acetyl transferase (ChAT) and decreased concentrations of acetylcholine (ACh) (Perry et al., 1977). The nucleus basalis of Meynert is involved in memory and attention (Düzel et al., 2010). The cholinergic hypothesis is based on these phenomena and states that the cognitive decline in AD is a consequence of the loss of cholinergic neurons. However, clinical studies have revealed that there is hardly any loss of cholinergic neurons in the early stages of AD (Davies, 1999). These findings challenge the cholinergic hypothesis. On the other hand, since cholinergic activity in the hippocampus declines from the fourth decade (Perry et al., 1992) and patients with AD are over 60 years old in 90% of the cases (Prince et al., 2016) it is likely that cholinergic depletions in the hippocampus are present in early stages of AD.

Another hypothesis about the neurological origin of AD is based upon its classic hallmarks: plaques and tangles, and is called the amyloid cascade hypothesis (Figure 2). The hypothesis proposes that accumulation of amyloid β (Aβ) plaques results in a cascade of processes that eventually lead to neuronal loss and AD (Selkoe, 2002). A plaque is an extracellular accumulation of aggregated Aβ in the brain parenchyma or vasculature. Aβ is a cleavage product of amyloid precursor protein (APP). The accumulation of Aβ is a result of either increased Aβ production, increased production of aggregation prone Aβ species or impaired clearance of Aβ. According to the amyloid cascade hypothesis the Aβ plaques ignite the widespread of neurofibrillary tangles (NFTs), which in turn are a more direct cause of neurological and synaptic damage (Selkoe and Hardy, 2016). NFTs are intra-neuronally accumulations of

abnormally phosphorylated tau. (Scheltens, 2016). In early stages of AD, a strong correlation exists between amyloid plaques and cognitive decline (Tomlinson et al., 1970; Nelson et al., 2009). Research also found a strong association between NFTs and cognitive loss (Tomlinson et al., 1970; Cummings et al., 1996).

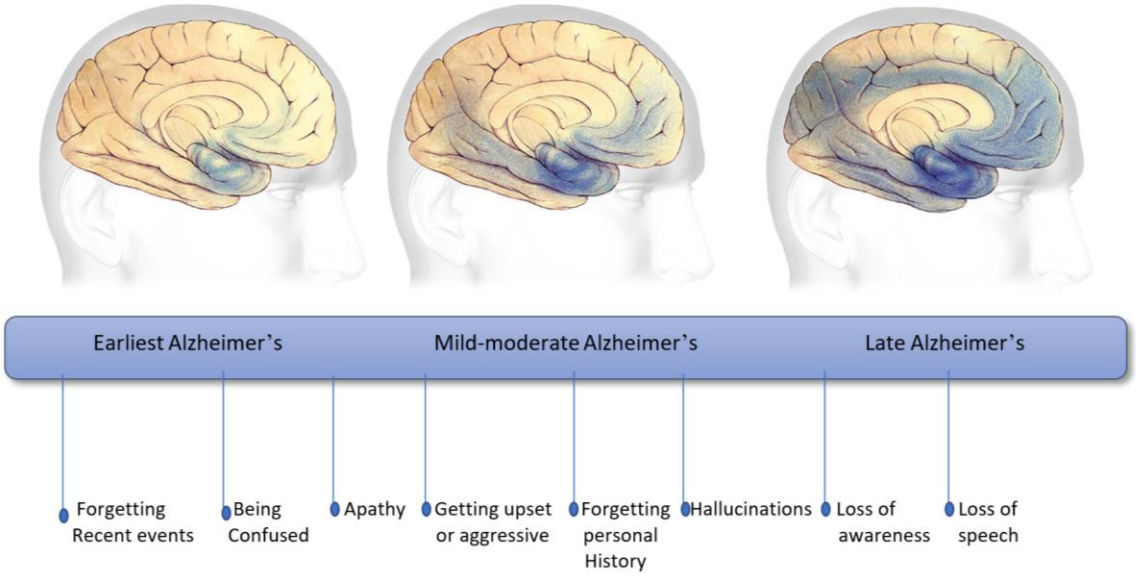

Figure 2: Spreading of plaques and tangles (blue haze) through the brain in correlation to behavioural symptoms of AD (Alzheimer's Association National Office; Alzheimer Nederland)

AD is associated with atrophy in several brain regions. Currently, magnetic resonance imaging (MRI) can be used to quantify in vivo neurodegeneration of cortical and subcortical grey matter (GM) regions and estimate white matter (WM) structural damage in AD (Pini et al., 2016). Hippocampal atrophy is a strong biomarker for AD, MRI studies found that the hippocampal volume is 15-40% smaller in AD patients than in healthy controls (Bosscher et al., 2002). Hippocampal volume is correlated with clinical decline and the severity of cognitive disorders and episodic memory deficits in AD (Jack et al., 2000; Sarazin et al., 2010).

The neocortex is affected in AD patients in a stereotypical manner. In early stages, cortical atrophy affects the medial temporal lobe, entorhinal cortex (EC) and hippocampus, hereafter the temporal-parietal-frontal trajectory is affected, and in the later stages, the motor areas (Apostolova et al., 2007; Prestia et al., 2010).

The EC connects the neocortex and the hippocampus (Insausti et al., 1995). Accumulation of NFTs occurs early in the EC (Braak and Braak, 1995), which may result in the disconnection of information from the neocortex to the hippocampus (Stoub et al., 2014). Impairments of this system are thought to be the cause of episodic memory decline (Nadal and Hardt, 2011). AD patients show more EC atrophy and less EC thickness compared to healthy controls (HC) (Dickersen et al., 2001; Blanc et al., 2015).

Not only the hippocampus and EC are affected in the early stages of AD, but also the amygdala, which shows NFT formation, atrophy and neuronal loss in AD patients (Scott et al., 1991). The amygdala plays an important role in encoding and consolidation through emotional stimuli and thus is a key factor in explicit memory (Hamann, 2001). Significant tissue loss was found in the nuclei of the amygdala

connected to the olfactory system and cholinergic pathways and to nuclei connected to the hippocampus (Cavedo et al., 2011).

The thalamus is important for directing attention, suppressing irrelevant stimuli and declarative memory functions (Newman, 1995; Van der Werf et al., 2000). The thalamus of AD patients was reduced about 12% (Zarei et al., 2010), especially the thalamic nuclei with connections to the hippocampus via the fornix and to the temporal and prefrontal cortices. These connections are essential for episodic memory (Aggleton and Brown, 1999).

The main nuclei of the basal ganglia are also affected by AD. The caudate nucleus is involved in attention, planning, execution of behaviour to achieve complex goals (Grahn et al., 2008), motor learning and forming associations for explicit memories (Nakamura et al., 2001). Research showed that the caudate nucleus in AD patients was lower in volume compared to HC and showed atrophy (Madsen et al., 2010). AD patients also show a reduced volume of the nucleus accumbens which is connected to the limbic areas (de Jong et al., 2012).

The only approved medication available for AD are acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonist memantine. Both drugs are symptomatically and do not address the underlying cause of the disease (Kulshreshtha and Pilani, 2016). Moreover, these drugs are only in high doses able to control neuropsychiatric symptoms but have a moderate effect on cognition. In some patients, the drugs do not have an effect at all (Tan et al., 2014). Furthermore, the side-effects of psychotropic drugs are potentially harmful for older patients with dementia and are associated with a poorer quality of life (Selbaek et al., 2007). Because of these reasons, nonpharmacological interventions are being studied intensively and evidence for the effectiveness of these therapies is growing. Several different nonpharmacological therapies have been proposed to improve cognitive, psychosocial and behavioural alterations in AD patients, but also to improve motor impairment, quality of life and so on (Gallego, 2017). The aim of this study is to describe the most recent studies that have investigated such a nonpharmacological therapy.

Results

Reminiscence therapy: Asiret & Kapucu, 2015

Reminiscence therapy it the most commonly used nonpharmacological therapy in AD. Reminiscence was described by Burnside and Haight: the process of remembering long-forgotten experiences and events that are worth remembering for the person (Burnshight & Haight, 1992). The effect of reminiscence therapy on cognition, depression, and activities of daily living for patients with AD was studied by Asiret and Kapucu. They included 62 AD patients over 65 years old, who had a cognitive score between 10-24 on the Mini-Mental State Examination (MMSE) test and were willing to communicate and participate in the study. The participants were randomly divided into two groups: intervention and control. Depression, cognition, and activities of daily living were evaluated before and after intervention. A conversation, lasting 20-25 minutes, was held with the control group subjects to ethically prevent interaction between the groups. The intervention consisted of 12 weekly sessions lasting 30-35 minutes in a group of 2-5 subjects. In each session, conversation was held with one subject of a group, who was asked to tell the group about memories or experiences of the past. Old objects and pictures were used during the session to facilitate remembering. The subject's recalled events were noted by the investigator. The results show a significant difference in cognition between control and intervention. A significant decrease of mean depression score was found in intervention group compared to control at

the end of reminiscence therapy. Mobility, feeding, sleeping, individual hygiene, and dressing were not changed in either group. In the intervention group, a positive but limited change in communication, collaboration, socialization and restlessness was found. The results are in line with earlier research (Chueh & Chang, 2014; Azcurra, 2012; Thorgrimsen et al., 2002). The effect of cognition is thought to be due to the conscious effort and time spend on remembering past events. The memories of another person may also stimulate the memories of individuals and facilitate reminiscence. During intervention, individuals communicate, talk without being criticized, get the notion they belong to a group and get an increased confidence because of recalled event. These factors will probably decrease state of depression and stimulate communication, collaboration and socialization.

Music therapy, Gallego & García, 2015

A study done by Gallego and García investigated the cognitive, psychosocial and behavioural effects of music therapy on patients with AD. Forty-two patients with AD were divided into two groups, based on the Clinical Dementia Rating (CDR) scale: CDR1 and CDR2. CDR1 consisted of patients within a mild dementia stage, while the patients in CDR2 were in a moderate dementia stage. Several neuropsychiatric, cognitive and functional assessments were done at three points during the study: before intervention, after 3 weeks of intervention and after 6 weeks of intervention. Twice a week, the patients underwent a therapy session of 45 minutes over a period of 6 weeks. Each session consisted of: a welcome song, rhythmic accompaniment by clapping hands or playing music instruments, moving to background music, guessing songs and interpreters and farewell song. Music therapy resulted in an improvement of attention, motor skills, orientation, language and memory, the latter three showing the biggest effect. Cognitive functioning improved progressively throughout the study, suggesting a long-term effect of music therapy. Language was only significantly improved in CDR2. In CDR2 also positive effects on delusions, hallucinations, irritability and agitation were found, this moderate dementia group scored higher in these domains at baseline compared to mild dementia. Both groups showed improvement of disinhibition, anxiety and depression. Progressive cognitive decline lowers the stress threshold, (Hal & Buckwalter, 1987), therefore stressful situations can result in agitation and aggressiveness. Music therapy increases the stress threshold, and thus reduces behavioural problems as agitation (Volicer & Hurley, 2003). Music can evoke pleasant emotions and effects the endocrine and autonomic nervous system by decreasing stress-related activation of the adrenomedullary and parasympatic nervous system (Suzuki et al., 2004). The small groups in this study promoted interaction and intimacy, which can improve patient's mood. These actions may explain why the music therapy had a large effect on anxiety and depression. Improvements in memory can be explained by the fact that familiar, favoured songs were used. Because AD patients can still recognise emotions in songs (Drapeau et al., 2009) this resulted in a rush of emotions and memories when the subjects heard the familiar music (Irish et al., 2006). Music enhances encoding of verbal information in healthy elderly and in AD patients (Simmons-Stern et al., 2010). This might be explained by the increased arousal and reduced anxiety that are brought about by music and which in turn promote encoding and attention (Soria-Urios et al., 2011). Another explanation is that music alters associative, executive and auditory networks that are involved in brain plasticity and learning (Trainor et al., 2009). The language improvement after music therapy can be explained by the fact that music can improve naming ability and speech fluency and content (Brotons & Koger, 2000). Music training leads to activation of areas in the right hemisphere involved in speech processing (Jantzen et al., 2014). Not all music therapy studies show improvements in cognition in AD patients (Sakamoto et al., 2013; Li et al., 2015). This might be due to differences in intervention type, for example, interactive music therapy was proven to be more effective than passive music intervention

(Sakamoto et al., 2013). Other differences to note are: individual versus group sessions and relaxing music versus pop music (*Gallego & García, 2015*). Further research with larger sample sizes will be necessary to clarify these differences.

Music therapy, Palisson et al., 2015

A research done by Palisson et al. used music as therapy in AD in a different way. The study was set to investigate encoding and retrieval of texts with a musical association versus texts presented with a non-musical association versus text presented alone in patients with mild AD and healthy controls (HC). 12 AD patients and 15 HC participated in the study. Familiar melodies were used as musical associations and familiar films were used as non-musical associations. Three texts were selected, all using ordinary vocabulary and rhymes but with different themes related to ordinary life. Two texts were spoken for the non-musical conditions and one was sung on a melody with instrumental accompaniment. All subjects were tested in one 90 minutes lasting session. During the coding state, each text was presented visually as well as auditory. In the non-musical association, a silent video and text were displayed split screen. First the whole text was presented to the subject, hereafter the text was learned line by line until the text was finished or until the subject could remember 60% or less of the learned lines. After this, a direct recall was conducted and after a 5 minutes delay, the subjects were again asked to conduct a free recall of the text. This delayed free recall score was used as an indicator of retrieval abilities. During the 5 minutes delay, standardized neuropsychological tests were conducted. HC scored better than AD patients in coding stage, immediate recall and delayed recall. Both HC and AD patients scored best with a musical association and worst without association in all phases. After a 5 minutes delay, all AD patients recalled more words in the musical association than in the non-musical association or without association. This effect was evident even if subjects did not score better with musical association during encoding stage. These results suggest that music can improve not only familiarity, but also recollection. Earlier research did not show an improvement of recollection with music, however in this study the music used was unfamiliar (Simmons-Stern et al., 2012). Familiarity of the music is likely to improve learning and retention (Purnell-Webb & Speelman, 2008). There are many hypotheses about why music enhances memory. First of all, music elicits emotion and emotion leads to better memorization (Kensinger & Corkin, 2003). Music can also increase psychophysiological activation which leads to a higher mobilization of attentional resources (Berger & Menon, 2007). Psychophysiological activation refers to physiological activation initiated by a psychological event, e.g. an increase in heartrate as a result of fear (Studer et al, 2014). Language and music overlap in the brain (Schöhn et al., 2010). A recent study showed that musical encoding facilitates the deactivation of the dorsolateral prefrontal cortex, a structure normally involved during encoding. It is suggested that music creates a richer encoding context, which results in the dorsolateral prefrontal cortex being superfluous (Ferrere et al., 2014). Music may stimulate memory by providing additional information about the text. Higher cognitive resources might be necessary in the encoding stage to form an associative link connecting two components. This results in a deeper encoding, which leads to better retrieval (Pavio, 1967). This dual-coding theory can also explain the higher scores with the non-musical association versus no association. However, according to the dual coding theory, one would score worse with music during encoding, which was not seen in this study. Some limitations need to be addressed. The rhymed text may have stimulated learning regardless of the condition. Also, the same texts were always used in the same condition, this opens up the possibility that the text with no association was simply harder to learn than the others.

Dog therapy, Swall et al., 2015

The aim of a study done by Swall et al., was to illuminate the meaning of the lives experience of encounters with a therapy dog for patients with AD. The researchers also investigated whether therapy dogs can evoke awareness of the past and present life of persons with Alzheimer's disease. Lack of awareness is a common symptom in AD. It is hypothesized that altered memory self-awareness in AD is associated with amyloid pathology (Vannini et al., 2017). Four women and one man with medium to severe AD were included in this study. All subjects were in the same nursing home and had never received dog therapy before. Data comprised of video observations (VIO's) of the therapy sessions. Each subject received 10 weekly visits, each visit lasting 30 minutes. A dog handler was present during the visit. The VIO's were viewed and transcribed into text that included verbal and non-verbal communication. The phenomenological hermeneutical research method was used to analyse the text. The text was first read several times, which formed a naïve reading. Then the text was divided and organised into meaning units, meaning units were condensed, compared and abstracted into subthemes. Subthemes were abstracted into themes, themes into main themes. Subthemes, themes and main themes were reflected upon to form a comprehensive understanding. The dog therapy seemed to create awareness with past and present existence in the subjects. The persons talked about memories and were aware of the situation in a more adequate manner than before. The dog seems to be a memory trigger for stories about earlier life. Subjects showed self-esteem when caring for the dog. The results might have been influenced by the fact that all subjects had positive experiences with dogs in earlier life. It might also have had an effect that the dog handler was in the room and asked questions to the subjects. This way of analysing data is time consuming and it is hard to maintain focus on the aim and stay truthful to the data. Moreover, it is impossible to obtain the whole experience of a person (Lindseth & Norberg, 2004) and there are always more possible interpretations than the interpretation of the authors (Ricoeur, 1979).

Paro-activity, Jøranson et al., 2015

As mentioned before, many AD patients show symptoms of depression and agitation (Bergh et al., 2012), a strong association exists between these symptoms in dementia and a poorer QoL (Beerens et al., 2013). In addition, people with severe dementia are often in a state of disinterest, inactivity and apathy. This leads to them spending most of the day doing nothing, this also results in a lower QoL (Kuhn et al., 2005). Assessments skills of QoL in AD are based on: competent cognitive functioning, the ability to engage in positive pastimes and in social activities, in addition to experiencing positive emotions and not being negatively affected (Lawton, 1994). Jøranson et al. investigated the effect of QoL of a robot-assisted group activity for people with dementia. The study consisted of a series of randomized controlled trials of group intervention with the seal robot Paro, this intervention is called Paro-activity. Subjects were assessed at baseline (t0), at the end of the 12 weeks of intervention (t1) and at follow up, three months after intervention ended (t2). Assessments

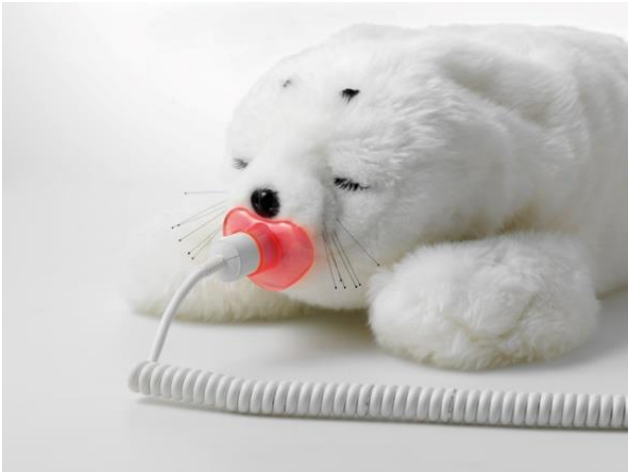

Figure 3: Baby seal Paro (Focal Meditech)

consisted of an agitation rating, a dementia severity measurement, a cognitive impairment rating and a QoL assessment. The study included 53 people with dementia or cognitive impairment who scored lower than 25/30 on the MMSE. 30 minute sessions were held twice a week, the sessions were held in a group with a maximum of 6 participants. During the sessions Paro was placed on each subject's lap for an equal amount of time.
A significant difference in QoL was found at t2 between intervention and control in patients with severe dementia. The control group showed a decrease in QoL, while the intervention group remained almost stable. No difference was found in patients with mild/moderate dementia. The lack of effect in mild/moderate dementia patients might be explained by the fact that they still have some control of life and can remain in interaction with others, which increases QoL in dementia (Moyle et al., 2011). In contrast to patients with mild/moderate dementia, patients with severe dementia are not able to perform daily activities due to severe cognitive decline. This results in a lower QoL (Lawton, 1994) through Paro-activity the patients are able to engage in positive pass time and have social interactions which increases QoL.

Doll therapy, Braden & Gaspar, 2015
Another behavioural study was done with doll therapy. The aim of the study was to evaluate the implementation of non-invasive evidence-based intervention of baby doll therapy on the occurrence of agitated behaviours of individuals with dementia. The project was held in a dementia care centre for Alzheimer's disease, the study included 16 female residents over 60 years old with moderate to severe dementia who stayed at the long-term care facility. All participants received a doll. The used dolls were safe to handle and realistically looking (Figure 4). The intervention lasted for two weeks. Nursing staff evaluated six areas of behaviour namely: activity/liveliness, interaction with staff, interaction with other residents, happiness/contentment, agitation and amenable to personal care. These areas were evaluated before and after intervention. The majority of the subjects showed a positive an overall trend for a positive change in behaviour. Only the level of happiness showed a significant difference between baseline and after intervention. Seven of the clients showed a ''little more'' happiness after intervention. The nursing staff described the therapy as being helpful in modifying many aspects of the residents' behaviour. Literature states that doll therapy can give a purpose to patients with AD and thus make them feel useful (Mackenzie & Mukeatova-Ladinska, 2006). It was intended that the evaluation before and after intervention of one subject was done by the same staff member, this was not always possible, which is a flaw in the experimental design.

Figure 4: Picture of the baby dolls used for the project (Braden & Gaspar, 2015)

Language-Enriched Exercise Plus Socialization, La Rue et al., 2015

A study done by La Rue et al. evaluated the effects of Language-Enriched Exercise Plus Socialization (LEEPS) on cognitive performance, physical fitness, and measures of well-being for persons with mild dementia. The study was done without control condition. Cognition, physical fitness, mood, and quality of life were assessed at baseline and at two follow-ups after 1 and 2 years respectively. Participants and volunteers were paired up and had a meeting twice a week. One meeting was for exercise and language stimulation of approximately 90 minutes, and one was for a social outing or volunteer work. The aim of the language exercise session was to stimulate sustained attention, deep processing of language and semantic content and production of verbal responses on demand. Analysis focused on change from baseline to follow-ups. 64 participants with AD or related disorders completed baseline assessments, 29 remained in the program till first follow-up and 8 participants completed the second follow-up. Only 5 participants engaged in volunteer activities next to the exercise plus language stimulation. The only parameters that changed significantly from baseline to intervention were the number of arm curls and QoL. The number of arm curls increased while QoL decreased. However, there were 3 individuals whose QoL decreased dramatically, when these subjects were excluded, there was no significant change in QoL. Even though there were no significant differences between baseline and intervention MMSE, there was a significant difference between first follow up MMSE and a calculated value of the expected MMSE based on longitudinal studies of AD patients. A similar pattern was found for other cognitive tests. No significant differences in cognition, physical fitness, or well-being between baseline and second follow-up were found. Most subjects remained stable in cognitive function, mood and physical fitness during both interventions, which is notable considering the progressive nature of AD. The intervention did also increase the subjects' exercise duration. Activities that increase heart rate and respiration rates have a marked benefit for brain function and cognitive performance (Voss et al., 2011). However, due to the absence of a control group, it cannot be concluded that the stabilization nor the improvement of certain parameters can be attributed to the intervention. Still, LEEPS might be a promising therapy for dementia, especially considering that it includes activities that are simple and easy to learn for volunteers and are engaging and enjoyable for participants.

Cognitive rehabilitation and cognitive-behavioural intervention, Kurz et al., 2012

Cognitive rehabilitation (CR) focuses on providing support in the management of day-to-day problems. Kurz et al. evaluated a combined CR and cognitive-behavioural (CB) intervention in patients with mild dementia with regard to feasibility in a multicentre setting, acceptance by patients and carers and efficacy. 201 patients with AD were included in a randomized, controlled trial, all having a MMSE score of at least 21 and a carer who looked after them several times a week. 1 hour weekly sessions were held for 12 weeks. Four treatment strategies were applied namely: external memory aids, introduction of daily routines, day structuring and activity planning and reminiscence. Each session focused on 1 of these strategies and was carried out individually by a behavioural therapist. Homework suggestions were provided to promote transfer to daily life and participants learned ways to implement strategies. Control condition was a non-standardized standard medical management for patients with early dementia. Assessments were made at baseline, postintervention (month 3) and follow-up (month 9). No significant treatment-related differences were found regarding carrying out activities of daily living, QoL, depression, behavioural disturbances and cognitive ability. However, in female participants a significant antidepressant effect was found after intervention. Care burden was increased in intervention group. At

follow-up patients in intervention group showed less deterioration of cognitive ability than control patients, however this difference did not reach significance. Previous studied did show significant effects of CR on memory functions and mood (Troyer et al., 2008). Some limitations might explain the results. First of all, the intervention might not have been personalized properly. Although individual needs and goals were included, the level of standardization may have been too high. Due to the broad focus of the intervention, it might have been hard to implement all strategies into daily life. Moreover, treatment-associated changes might have been too small to show an effect in the assessments and more sensitive assessment strategies might be useful. Furthermore, intervention might have been too short.

Discussion

Worldwide, nearly 44 million people have AD or related dementia. This number is expected to triple during the coming 35 years (Prince et al, 2016). It is expected that in 2030 AD will be the seventh highest cause of death in high-income countries (Mathers et al., 2006). The disease has a progressive character and is associated with cognitive decline and several neuropsychological disturbances like agitation, anxiety and depression. QoL decreases in AD. The medication that is currently available is symptomatic and is limited to delaying the progression of symptoms by several months (Qaseem et al., 2008). For this reason, there is growing attention for nonpharmacological treatments. There is need for nonpharmacological treatment that helps patients cope with functional and emotional consequences of AD. Ideally, therapy would also improve functional ability, enhance activity and enable patients in attaining personal goals. (Bouwens et al., 2008). Some studies have also found a beneficial effect on cognition (Bayles & Kim, 2003). This study evaluated eight of the most recent studies on nonpharmacological therapies in AD. Reminiscence therapy showed a positive effect on cognition as well as depressive symptoms and is therefore very promising. The music therapy study done by Gallego and García found an improvement in attention, motor skills, orientation, language and memory. Cognitive functioning improved progressively throughout the study, suggesting a long-term effect of music therapy. However, other studies on music therapy found contradictory results regarding cognition. These differences are likely due to differences in intervention type, for example: passive vs interactive intervention and group intervention vs individual intervention. Palisson et al. found that providing a musical association during learning, can improve not only familiarity but also recollection. They also found that a non-musical association also promotes memory but to a lesser degree than a musical association. The therapeutic value of this study on the other hand, is not as clear as in the other studies. Swall et al. found that dog therapy seemed to create awareness with past and present existence in the subjects, still their results are based upon interpretation. Paro-activity can increase QoL in patients with severe dementia and patients showed an increase in happiness after doll therapy. Especially doll therapy is easy and cheap to implement in nursing homes, even so, not all AD patients react in a positive manner to the therapy and the nursing staff should take responsibility in this case. Paro-activity is somewhat harder and more expensive to introduce in a nursing home, but still can be implemented quite easily. Language-Enriched Exercise Plus Socialization was able to stabilize cognitive function, mood and physical fitness, however due to the lack of a control group no hard claims can be made. Cognitive rehabilitation (CR) and cognitive-behavioural (CB) intervention was able to decrease depressive symptoms in female participants but had no effect on carrying out activities of daily living, QoL, behavioural disturbances and cognitive ability.

Although some of the studies showed promising results, further research will be necessary to validate these results. Validations are necessary considering some studies did not include a control group and

most studies had small sample sizes and were conducted in a short time interval. Most studies evaluated before and directly after intervention. Only the study on Paro-activity and the study on CR and CB included an evaluation several months after intervention ended. For the other studies, it remains unclear if the effects of intervention remain in the long term. It is possible that the effects are temporary and only present directly after intervention. Some of the discussed studies had a session once a week, others twice a week. Session duration varied between studies, the shortest lasting 30 minutes, the longest lasting 90 minutes. None of the studies support their choice of session frequency nor duration. Furthermore, more attention must be paid to potential mechanisms of action and brain areas involved in certain therapies. Even though nonpharmacological therapies seem promising in improving QoL, cognition, motor-skills, awareness etc. it should be mentioned that it might be difficult to improve everyday functioning in AD patients. The study of Kurz et al. found no improvement in managing day to day problems after CR and CB intervention, which also supports this claim. Impairments in executive ability in AD patients compromise complex activities of daily living and hamper abilities to adopt novel coping skills, select relevant solutions and apply strategies in daily life. Treatment should therefore be highly personalized and only focus on a few personal needs (Kurz et al., 2012).

Personally, I think it would be interesting and promising to combine some of the interventions to increase the effectiveness. Especially the combining of a therapy that is focused on improving cognition with a therapy that is focused on improving QoL seems promising to me, because QoL and cognition affect each other. Patients with severe dementia can no longer perform daily activities due to cognitive decline, which leads to a lower QoL (Lawton, 1994). And, as mentioned earlier, a strong association exists between depression and a poorer QoL in dementia (Beerens et al., 2013), in depressive illness an impairment of cognitive function occurs (Austin et al, 1992). A promising combinative-therapy might therefore be reminiscence therapy, which mainly focuses on cognition, combined with Paro-activity which focuses on QoL. Since QoL and cognition are highly correlated, combining these two treatments into one therapy will not only combine the treatments' effects but the effects may also reinforce each other.

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