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The Effects of Animal-Assisted Therapy in Older Adults with Dementia

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Introduction

Millions of American older adults have dementia diagnoses and these rates continue to rise annually. Alzheimer's disease, a type of dementia, affects 1 in 10 adults over the age of 65 and is the 6th leading cause of death in the United States (Latest Alzheimer's Facts and Figures, 2016). Dementia primarily affects older adults and patients with these diseases are found in a variety of settings, including in their homes, assisted living facilities, care centers and hospitals. It is important for clinical social workers to note that although there is no cure for these diseases, there are therapies that can be employed to assist with both mood and cognitive function.

Animal assisted therapy is a therapeutic intervention that couples a trained mental health professional with an animal for the treatment of the patient. This therapeutic approach has been used in a variety of forms for over two hundred years and has had increased research into its effects when utilized with older adults (Reevey, 2010). Today, animal assisted therapy is employed in various settings, including in clinic environments, nursing homes and day programs, making it accessible to more patients than years prior. This systematic review will examine the benefits of animal assisted therapy in patients with dementia and the areas in which it is most beneficial to the patient.

Background

Dementia is a brain disease that affects tens of millions of individuals globally (Latest Alzheimer's Facts and Figures, 2016). Dementia, the broadest term for brain diseases marked by a functional decline in overall cognition and memory, can progress at different rates for those effected. To diagnose specific types of dementia, a medical professional may utilize brain imaging, cognitive tests/assessments and consider a patient's history. Within the category of dementia are well-known diagnoses including Alzheimer's disease, dementia with Lewy-Body and dementia caused by Parkinson's disease. Additionally, there are dozens of lesser known subgroups including vascular dementia and substance-induced dementia (Siberski, 2012). All dementia diagnoses indicate memory loss and impairment and can affect other functions of the brain including, executive functioning, critical thinking and word finding at various rates and severity. Dementia in all forms is most frequently diagnosed in the older adult population, with young onset dementia indicating that symptoms began before the age of 65 (Quinn, 2013).

There are currently five million people who are living with dementia in the United States and this number is expected to rise as the population continues to age (Latest Alzheimer's Facts, 2016). Currently 33% of older adults who die of any medical condition or of advanced age, die with diagnoses of dementia, indicating that our oldest and sickest population are deeply affected by the disease (Latest Alzheimer's Facts, 2016). In addition to the sheer number of individuals who are living with the progressively degenerative brain disease, there are family members and caregivers who work to ensure their loved ones receive appropriate care. This burden is both highly emotional and financially straining for families and communities. It is estimated that in 2017, dementia will cost the United States nearly $260 billion dollars (Latest Alzheimer's Facts,

2016). Dementia is not only emotionally taxing and draining on patients and families living with the disease, but on the resources of the nation as well.

In addition to the financial burdens of the disease and irreparable cognitive changes, these brain diseases can have devastating effects on the patient's mood and mental health. Researchers Knapskog, Barca and Engedal (2013), found that about 50% of patients with dementia will experience depressive symptoms throughout their disease progression. This rate is drastically higher than that of cognitively health older adults, whose rate of depression is estimated at 5-25% (Staab & Evans, 2000). The difference in rates of depression indicate a need for professionals working with this population to be assessing their patients for mood disturbances and changes and be aware of this increased risk. Not only is it important for individuals working with older adults to know the risks and rates of dementia, it is also important to recognize the depression and other mood concerns that are associated with these illnesses.

There is no cure for dementia in any of its forms, leaving families and patients to wait out the progression of the disease (Latest Alzheimer's Facts, 2016). While researchers worldwide have committed to working towards effective treatments to slow the cognitive decline and look for cures, families and caregivers are left to try to navigate current treatments and comfort measures as they are today. Today, the primary treatments are therapeutic interventions that "are targeted to treat symptoms or to improve cognitive function" (Buckley & Salpeter, 2015). These interventions include the use of prescription medications as well as non-pharmacological interventions. The non-pharmacological interventions aim to keep patients engaged and utilizing their memory, decisions making and executive functioning skills to the best of the person's ability. The prescription medications that have been approved for use in this population have varied amounts of research completed on their effects with equally varied results. Buckley &

Salpeter (2015), found that cholinesterase in-hibitors (ChEIs) have demonstrated to be beneficial in the slowing of the progression of the disease but its effects can only be seen for 1-2 years. Additionally, ChEIs drugs can only be utilized by individuals who have recent diagnoses of either Alzheimer's or dementia with Lewy Body and cannot be utilized in patients with other forms of dementia (Buckley & Salpeter, 2015). This research indicates that for many patients this is not an option based on their diagnosis and only provides temporary benefits to those who have qualified for use of these prescriptions.

There has been increased interest in non-pharmacological treatments for dementia in the medical community related to the low effectiveness of the medications that are currently available (Takeda, Tanaka, Okochi & Kazui, 2012). The available non-pharmacological treatments may be appropriate for patients at varying rates, based on their current state of cognitive ability, their preferences, and access to resources. These interventions include cognitive training, sensory stimulation, reminiscence therapy, validation therapy and animal-assisted therapy (AAT) (Takeda et al., 2012). This research will focus on the use of animal-assisted therapy and the benefits that it provides to dementia patients.

AAT has roots as far back as the 1800s, when the founder of an English facility for mental illness utilized farm animals to increase the quality of life in the patients (Reevey, 2010). AAT utilizes a variety of animals, from common household pets such as cats and dogs to more exotic animals like dolphins and birds. Reevey notes, "AAT means that a certified therapist or health care professional is using an animal as an aspect of treatment for an individual in an individualized, written treatment plan with specific goals" (2010, p. 68). The therapist or health care professional can structure his or her work with the patient in various ways, including

focusing the session on the interaction between patient and animal, or simply having the animal present for the interaction between patient and provider.

AAT has been utilized with older adults for nearly 30 years and has recently come to be considered a scientifically researched or evidenced based intervention, instead of being an anecdotally successful intervention (Mercer, 2015). AAT is used with older adults for various reasons including to decrease feelings of depression or loneliness by fostering companionship and the release of endorphins to increases the patient's mood (Mercer, 2015). While the effects of AAT have been studied extensively in older adults, there have been recent studies that work to demonstrate the implications in dementia populations. These studies have focused on benefits as well as the risks and implications for practice, all of which will be explored through a systematic review of the available and applicable literature.

The Impact for Social Workers

For clinical social workers, the implications of this research may be unending. Not only are social workers often resources for families and patients with questions about their dementia diagnoses, clinical social workers may also be the practitioners who are providing the non-pharmacological interventions. These interventions may take place in an outpatient setting such as a neurological clinic or individual therapy setting. They also may take place where the patient is residing, such as an assisted living facility, memory care or skilled nursing facility.

Methods

The methodology that was used to identify benefits of animal-assisted therapy in older adults with dementia was that of a systematic literature review. A systematic review is completed by employing a specific set of criteria and techniques when gathering research and the analysis of data within the articles. This is done to ensure that the biases of the author are not seen in the literature selected and this research is completed with the intention of bringing themes of various pieces of literature together in an organized and concise manner. Systematic reviews are designed to be replicated by other researchers and the protocol is laid out in a way that makes that possible.

Search Strategy

Databases that were used to identify the articles in the systematic review included PsycInfo, SocINDEX, Social Work Abstracts, PUBmed and Consumer Health Complete. Searches included the following terms: animal assisted therapy, pet assisted therapy, dog therapy, dementia, Alzheimer's, cognitive impairment, benefits, and effects. After locating the initial articles that met the above criteria, the abstracts of the articles were reviewed to determine if they met the demographic, age and methodology requirements.

All sources that are included are specific to the population of older adults with dementia and the intentional use of AAT. Articles included in this systematic review were completed between 2002 and 2017. This limitation was included to ensure that the most accurate and current information is reflected in the systematic literature review. Both quantitative and qualitative research were included in the searches as to not leave out valuable information that may have been compiled using either method.

The initial gathering of articles yielded 24 studies. These initial articles were selected after reading the abstracts to see if they appeared to fit the intention of this systematic review. Articles that did not utilize animals in a structured, therapeutic setting but instead as companions, were excluded from this systematic review. After the initial search and compilation of articles, there was a second review of articles where the methods sections were more closely reviewed and resulted in additional exclusions. Upon further review of the initial articles, five were excluded as they were found to be reviews of literature instead of individual studies and three were excluded due to their primary methods were comparing live animal assisted therapy to patient interaction with stuffed or robotic animals. With the exclusion of these eight articles from the original data set, 16 articles were left to be included in data abstraction and analysis.

Data Abstraction

Upon finalizing the articles to be used for the systematic review, data abstraction occurred, and details of the articles were placed into an organizational grid. Sample size and participant demographics of each study were extracted including severity of dementia ranging from minimal to severe, and living arrangements of participants. Additionally, research question, measures used, study type, assessment tools and findings were recorded in this organizational tool. Once these data points were extracted and placed into the organizational grid, a highlighting and theme mapping technique was utilized to begin to analysis the findings of the studies.

Analysis

To identify themes across studies, findings were organized in a chart based on what the findings were within each of the 16 studies. Articles with similar findings were placed under the appropriate header to note the prevalence of a given finding across articles.

In addition to the completion of the grid which was created during data abstraction, each article was also give a quality rating to indicate the level of rigor used in each study. Table 1 below shows the scoring criteria for the quality scoring. Possible total scores were between three and nine, with nine representing the most rigorous studies and three representing studies with lower scores and fewer study/subject requirements.

Table 1. Quality Rating

Method ↓	**1 (Poor)**	**2 (Moderate)**	**3 (High)**
Sample Size →	1-10	11-25	26+
Sampling Strategy →	Convenience/Snowball	Matched	Random
Comparison →	None	Non-Equal Groups	Randomly Assigned

The quality scoring of articles within themes are noted within the findings section. The average quality rating of the whole article set used in the analysis process was 6, indicating that this research set was of moderately rigorous quality.

Findings

When reviewing the findings and discussion sections of the final 16 empirical articles, themes became evident across studies. There were many interesting findings from researchers studying the effects of animal-assisted therapy with patients with dementia, but three primary themes came to light. These themes are: the effects of AAT on agitation, AAT's impact on decreasing depression; and AAT's impact on increasing motor activities in the participants of the studies. There were also outliers that were found when analyzing the research findings, and those will also be represented in this section.

Impact on Agitation

Four studies analyzed during this systematic review process found the use of AAT to be effective in decreasing agitation in dementia patients. A fifth study had mixed reports of AAT's effect on behavior and a final article found that the therapy had a negative impact of patient behaviors. The average quality score of the articles that examined the effects of AAT on agitation and behavior is 5.6, indicating that they are of moderate rigor. Table 2 below provides information about the articles that fit within this theme.

Studies with Findings Related to Agitation

Table 2

Author(s)	**Living Arrangements**	**Level of Cognitive Impairment**	**Findings**	**Quality Score**
Dabelko-Shoeny, et al. (2014)	Community Dwelling Members of Adult Day Program	Early-Moderate	Overall decrease in problem behaviors (including wandering) in participants after Equine Therapy including lower than that of the comparison group who received standard therapeutic recreation services.	7
Majic, et al. (2013)	Nursing Home	Severe	Agitation/behaviors remained constant for those receiving both AAT and other therapeutic recreation, while the same that received only therapeutic rec. saw an increase in behaviors/agitation over time.	9
Nordgren & Engstrom (2014)	Nursing Home	Moderate-Severe	Decrease in physical behaviors immediately following group AAT with increase in verbal agitation immediately following.	5
Richeson (2003)	Nursing Home	Moderate-Severe	Agitated behaviors decreased immediately following the intervention	3
Sellers (2006)	Nursing Home	Moderate-Severe	Decrease in behavioral agitation	3
Tournier, Vives and Postal (2017)	Nursing Home	Severe	Increase in negative affect (aggressive behavior and anxiety)	4

It is not uncommon for individuals with diagnoses of dementia to experience agitation or behavioral disturbances. Studies indicate that these behaviors, which may be manifested as verbal or physical outbursts, will affect up to 80% of diagnosed patients throughout their disease

progression (Nordgren & Engstrom, 2014). This statistic indicates that those who care for older adults with dementia are not only faced with the forgetfulness or disorientation of those they're caring for but may also be attempting to manage unwanted or inappropriate behaviors related to their disease.

Three of the four studies that demonstrated a positive impact on behaviors and agitation found a decrease, either from the patients' baseline or in relation to the comparison group (Dabelko-Shoeny, et al., 2014; Richeson, 2003; Sellers, 2006). The fourth study found that the behaviors of the patients receiving animal assisted therapy remained constant compared to their baseline measures, while the comparison group which was receiving alternate, non-animal based therapeutic recreation, saw an increase in unwanted behaviors and agitation over time (Majic, et al., 2013). The participants of the Majic et al., (2013) study were patients with severe dementia as evidenced by a medical diagnosis and score on the Mini Mental Status Exam, which is a standardized test of cognitive ability/impairment.

It is important to note that one study found that AAT had a negative impact on patient behaviors and another indicated mixed results on overall agitation of participants (Nordgren & Engstrom, 2014). Researchers studying group AAT with patients with moderate to severe dementia showed that caregivers observed a decrease in non-aggressive physical behaviors, such as wandering or attempting to get out of bed, directly following the session Nordgren & Engstrom, 2014). The same caregivers also reported an increase of verbal behaviors or agitation immediately after the intervention (Nordgren & Engstrom, 2014). Another study found that patients were found to have a more negative affect following group AAT which included an increase in "anxiety and aggressiveness" (Tournier, Vives & Postal, 2017, p. 56). These researchers have theorized that the increased agitation may have been caused by the group

setting in which the therapy was delivered and noted the need for increased research to determine the root cause of the behaviors (Tournier, Vives & Postal, 2017). It may be significant to future research that the Tournier, Vives & Postal study used group AAT with patients with severe cognitive impairment which may have also contributed to their outlier findings.

Impact on Depression

In addition to the impact of AAT on agitation and behavioral symptoms, there were also five studies that found that individuals who received AAT had decreased rates of depression. The average quality rating of these five studies is 8.6, indicating that these studies were of high quality, many of which included large sample sizes and control groups. These high-quality studies observed participants from various settings. Three studies utilized participants who resided in nursing homes while one looked at residents in an assisted-living facility, and one looked at members of an Alzheimer's specific adult day center (Majic et al, 2013; Olsen et al, 2016; Travers, Perkins, Rand, Bartlett & Morton, 2013; Friedmann et al., 2015; Menna, Santaniello, Gerardi, Di Maggio & Milan, 2016). The studies explored the impacts on patients across settings and included patients with mild to severe dementia.

Studies that Found AAT Decreases Depression
Table 3

Author(s)	**Living Arrangements**	**Cognitive Impairment**	**Findings**	**Quality Score**
Friedmann et al., (2015)	Assisted Living Residents	Moderate-Severe	Depression rates (Cornell screening tool) decreased more throughout the intervention time in the group receiving pet-therapy vs. the group participating in reminiscence.	9
Majic et al., (2013)	Nursing Home	Severe	Residents receiving AAT had decrease in Dementia Mood Assessment Scale (DMAs) score during post-test while the control group experienced an increase in this score over time.	9
Menna, et al. (2016)	Alzheimer's Specific Day Center	Mild-Moderate	Statistically significant decrease in Geriatric Depression Score (GDS) for those who received AAT-group receiving reality orientation therapy also saw a decrease but by fewer points.	8

Olsen et al., (2016)	Nursing Home	Mild-Severe	AAT group had clinical improvement on depression scale when measured at baseline and 12-weeks after the intervention ended for those with severe dementia.	9
Travers et al. (2013)	Nursing Home	Moderate-Severe	Greater decrease in depression for those who participated in AAT vs. those who participated in human only therapy.	8

The studies in which these results were found used various tools for measuring depression at baseline and post AAT. Three studies utilized the Geriatric Depression Scale (GDS), a depression scale formulated for specific use with older adults, one study used the Cornell Scale for Depression in Dementia (CSDD) which is completed by caregivers of individuals with impaired cognition, and one study used the Dementia Mood Assessment Scale (DMAs) which is a scale that assesses both participants' mood and cognitive impairment. In all five studies, the depression scales were completed prior to the introduction of AAT as a baseline measure of participants. These scales were then completed again, either during the intervention period or after the AAT was completed. The timing of the retest was based on the goals of the study, either examining the immediate effects of AAT or the lasting effects of AAT.

These studies demonstrated that AAT interventions impacted participant depression rates as evidenced by patients scoring less on the respective depression scales used to monitor mood. The study completed by Olsen et al., (2016) noticed this change only in their sample participants with severest levels of cognitive impairment, and could not generalized their findings to their participants as a whole. These researchers randomly assigned participants residing in nursing homes to either receive animal assisted interventions or the standard non-pharmaceutical interventions that are standard to the care center which included music therapy, structured crafts and reminiscence groups. The intervention lasted 12 weeks with participants receiving 30 minutes of AAT two times throughout the week. The CSDD was completed with participants

prior to starting the intervention, during the intervention and 12 weeks after the intervention had stopped. The administration of CSDD during the intervention found a statistically significant decline in CSDD score for individuals with severe dementia, which indicates decreased depression. This result was not found in individuals with mild to moderate dementia or in the control group who in fact had an increase in the CSDD score.

Impact on Motor Ability

In addition to the behavioral and mood themes found within the 16 articles utilized in this systematic review, four articles revealed the impact of AAT on motor functioning and physical ability. The average quality score of these four articles is 5.75, which is slightly below the average of the complete article set, but is close to the quality rating of the articles that indicated AAT's impact on behavior and agitation. Of these four articles, two of the samples were community dwelling members of adult day programs, one sample was comprised of individuals residing in assisted living settings with the final study focusing on nursing home residents.

Studies that Found an Impact on Motor Ability
Table 4

Author(s)	**Living Arrangements**	**Level of Cognitive Impairment**	**Findings**	**Quality Score**
Dabelko-Shoeny, et al. (2014)	Community Dwelling Members of Adult Day Program	Early-Moderate	Several participants who typically needed assistance attempted to be independent or voice interest in standing, walking etc. Therapy horse was thought to motivate the participants to be increasingly physically active.	7
Friedmann et al., (2015)	Assisted Living Residents	Moderate-Severe	A roughly 3.5% decrease in individuals who spent less than 1% of their time doing at least moderate physical activity 3-months after AAT finish, compared with a less than 1% decrease in the control group.	9
Mossello et al., (2011)	Adult Day Program	Severe	Periods of AAT were found to have increased motor activity as evidenced by increased motion and interaction with environment throughout intervention period compared to the motor activity observed throughout time of control activity.	4

Nordgren & Engstrom (2012)	Nursing Home	Severe	Single subject was needing assistance with ambulation prior to AAT but three months after the study was able to ambulate and move about her environment independently.	3

The research completed by Dabelko-Shoeny et al., (2014) was the only in the article set to utilize horses in AAT, and found the unexpected results of increased physical movement through the intervention. In this study, participants were transported to a barn and were taught and encouraged to care for the horses which may include brushing, saddling or walking the animals. Adult day staff observed that some participants who previously had low motivation to participate in physical activity or required/requested assistance to stand or ambulate, were doing these things independently when in the presence of the horse (Dabelko-Shoney et al, 2014). This was not an intentional finding of the study so there is not numerical data available to demonstrate rates in which this occurred, but the researchers have noted the interest for future research specific to the use of horses in AAT for motor function.

The three other studies were purposeful in their observation of participants' movements and ability to complete activities of daily living (ADLs). The findings of one study indicated clearly the physical impact of this intervention, "…40.9% of the participants in the…intervention group and 38.9% of those in the reminiscing intervention group spent less than1% of their time in moderate or greater physical activity. After three months of intervention, 36.8% of the participants in the…intervention group and 37.5% of those in the reminiscing intervention group spent less than 1% of their time in moderate or greater physical activity" (Friedmann et al, 2014, p. 282). This demonstrates the greater effect of AAT on the physical participation of dementia patients compared to the physical impacts of the reminiscence group. Two other studies found similar increases in physical or motor activity. One noted the ability for the participant to

ambulate without assistance three months post intervention while the other noted an overall increase in physical movements and motion during the AAT intervention (Nordgren & Engstrom, 2012; Mossello et al., 2011). This theme was the least expected of the three themes found across works, and provides the foundation of continued research related specifically to the impact of AAT on the physical activity level and abilities of individuals with dementia.

Outliers

In addition to the themes that were found across articles in this systematic review, there were studies that produced interesting results that were outside of the themes identified above. Two studies found that study participants who received AAT had an increase in engagement with their environment and with their peers (Marx, et al., 2010; Olsen, Pedersen, Bergland, Ender-Slegers, & Ihlebæk, 2016). The average quality rating for these two articles is 7.5. The study completed by researchers Olsen et al., (2016), demonstrated that patients with dementia had increased engagement in their environment by way of not only interacting with the dog, but having increased interaction with the other group participants and the dog handlers.

Another outlier that was found in various research studies was the effect of AAT on quality of life (QOL). Three studies looked at the impact of AAT on (QOL) for nursing home residents with dementia. The average quality rating score for these three articles is 6.7. Research completed by Nordgren & Engstrom, (2014) tasked nurses at the nursing home with documenting observable behaviors in participants to measure patients' QOL at baseline and one week after the intervention had occurred. Of the nine participates that completed the study, QOL was found to improve, with nurses charting that the patient's exhibited more enjoyment (Nordgren & Engstrom, 2014). These QOL findings are important for the exploration of future

uses of AAT, but were not included in the findings section of this systematic review due to their being fewer articles with these results that the other themes.

Discussion

This systematic review has revealed many benefits of AAT when used with patients with dementia diagnoses. The implications of these findings can be utilized by clinical social workers and embraced at the micro, mezzo and macro level and across the systems that individuals and their families may be involved.

At the micro level, it has become clear that there are personal benefits for individuals receiving AAT. With findings demonstrating an increase in quality of life, decrease in depression, decrease in agitation and increase in motor ability, there are many practical and measurable benefits for the use of AAT with older adults experiencing dementia. There are alterative non-pharmaceutical interventions that can be employed with this population, but the research completed specific to AAT highlights the evidenced based nature and expected benefits for those participating. Additionally, the research can be used to encourage clinical social workers, and other licensed therapists, working with this population to explore the needed qualification and skills to be a provider of this intervention.

On the mezzo level, the results of these studies can provide comfort and assurance to the families and loved ones of those effected with cognitive deficits and dementia. Family members may be able to advocate for this interventions as an alternative to pharmaceuticals, which are expensive and demonstrate limited, temporary reprieve of dementia symptoms (Buckley & Salpeter, 2015). Of additional benefit for individuals and families working to support older adults with dementia is to know that there were positive outcomes found regardless of severity of

dementia. This can indicate that AAT can be used with older adults at any stage of the disease, or throughout their disease progression with benefits throughout. Additionally, agencies that work with this population should look at implementing AAT in programing. The systematic review looked at this intervention's use in assisted living facilities, adult day centers and nursing homes. It may also be beneficial for individual therapists and group therapists to explore the implementation of AAT as a therapeutic intervention in work with patients with dementia.

At the macro level, it would be important for large, national organizations such as the Alzheimer's Association to make known the benefits of AAT. This would increase the visibility of these programs and be a great resource for families and providers. In addition to visibility and understanding of AAT as a therapeutic option, it is important that we consider payment for these services. While information about insurances paying for AAT with dementia patients was difficult to locate, a non-profit organization that focuses on the benefits of AAT with autistic children found that only 12% of recipients had their therapy paid for by insurance (IAN Research Findings-Animal Assisted Therapy, 2011). To ensure this evidence based intervention is accessible to those who may benefit, insurance companies, Medicare included, need to offer reimbursement to trained therapists who offer AAT.

With our aging population and the high rates of which dementia effects older adults, it is imperative that society explore ways to best serve this population. Research results have indicated the worth of AAT as a non-pharmaceutical option to decrease depression, agitation and increase motor function and quality of life. It is important that research about AAT and its effect on individuals with dementia continues and focuses on the ways that various animals may enact various results and cost versus benefit compared to other non-pharmaceutical approaches.

Additionally with advocacy for the benefits and need for payment, AAT can be a realistic intervention of millions of Americans.

Limitations

One limitation of this study was the inconsistency of language used to describe animal-assisted therapy across articles. There are many studies that include varying terms for animal-assisted therapy including animal-assisted intervention, animal-assisted activity, etc. While the review of the methods section made it clear if these articles with differing terms met the requirements of occurring in a structured setting with a trained therapy provider, it added a layer of complication and confusion to the initial searches for this systematic review. Another limitation is that many of these studies were completed in European countries. While these articles were useful for this systematic review, it raises some question as to why there were limited studies completed in the United States.

There was also limited information available in the studies about the participant's prior experience with animals. It may be important to understand the effects of AAT on individuals with varying histories and interactions with animals. To understand the relationship the participant had with animals prior to their onset of dementia may indicate if history or experience impacts results.

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Note: references marked with an asterisk (*) indicate studies included in the systematic review

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