8-20-2017

Pharmacological and non-pharmacological management of depression in patients with Alzheimer's disease

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Abstract

Reflecting the most present evidence based knowledge, the most current edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) has taken a major step of redefining Alzheimer's disease and other types of dementia as minor or major neurocognitive dysfunctions. The American Psychiatric Association (APA) changed directions of viewing Alzheimer's disease (AD) from a condition characterized by deficit in function to a condition characterized by decline in function. This opened the door to view AD and other comorbid disorders of AD (like depression) through the lenses of prevention and treatment. Treatment of depression in individuals with Alzheimer's disease is aimed at preventing decline in function. The prevalence of depression in AD is alarming (Di Iulio et al., 2010) and new cases of AD are rising annually (CDC, 2016). Therefore, there is an ongoing need for practitioners educated in caring for people with Alzheimer's disease suffering from depression. Advanced Practice Psychiatric Nurses (APPNs) have an exceptional position to provide comprehensive mental health care for this population of interest. To facilitate this knowledge, a review of the literature on pharmacological and non-pharmacological treatment of depression in AD was conducted using a relevant database (CINHAL, Cochrane, PubMED, PsychInfo, PsychiatryOnline) focusing on results from 2007 to the present. A search of prominent health agencies in North America and Europe for current guidelines reflecting the care of treatment of depression in AD individuals was also undertaken. This paper provides a synthesis of literature related to pharmacological and non-pharmacological treatment for depression in patients with Alzheimer's disease, including crucial information regarding a nursing standard of care that APPNs should provide for this population.

Pharmacological and non-pharmacological management of depression in patients with Alzheimer's disease

Depression is recognized as one of the most common comorbid psychiatric disorders of Alzheimer's disease (AD). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes AD as a type of major or mild neurocognitive disorders (NCDs). The American Psychiatric Association (APA) replaced the previously used term "dementia" with major or mild neurocognitive disorder to put emphasis on decline in function rather than deficit in function. DSM-5 recognizes major depressive disorder (MDD) as one of differential diagnosis of AD (American Psychiatric Association, 2013). Evidence shows that a prolonged history of major depression is associated with increased risk of developing Alzheimer's disease (Diniz, Butters, Albert, Dew & Reynolds, 2013). Furthermore, symptoms of depression and AD overlap significantly (Starkstein, Mizrahi &Power, 2008) and there are no validated instruments to add in prevention and treatment of Alzheimer's disease and also depression in AD (Cherbuin, Kim & Anstey, 2015).

Despite currently available treatments for depression, depression in Alzheimer's patients continues to be associated with greater disability and burden of care (Black &Almeida, 2004), decreased quality of life for patients (Leon-Salas et al., 2013) and increased morbidity and mortality (Barca, Engedal, Laks & Selbaek, 2010). Evidence shows that standard antidepressants are not effective when it comes to treatment of depression in AD (Rosenberg et al., 2010; Orgeta, Tabet, Nilforoorshan & Howard, 2017) and could be related to earlier cognitive and functional decline (Rosenberg et al., 2012). McCutcheon et al. (2016) suggested that the mental health burden due to depression in Alzheimer's disease is so high that it requires development of new ways of treatment of depression in AD.

Alzheimer's disease (AD) is a major public health problem and it affected 5.4 million individuals in 2014 in the United States. According to the Center for Disease Control and Prevention this number is projected to reach 13.8 million people in the US population by 2050 (CDC, 2016). The epidemiology of depression in AD has varied between different studies but it is estimated that it occurs in up to 50% in population of interest (Di Iulio et al., 2010). The Alzheimer's Association (Alzheimer's Association, 2017) estimates that Medicare and Medicaid will spend 68 percent of total costs on treatment of patients with AD and other dementias in 2017 and these costs will increase over 300 percent by 2050.

Purpose

The new DSM-5 emphasizes that Alzheimer's disease diagnosis, which is a type of major or mild neurocognitive disorder, is characterized by decline in a function (American Psychiatric Association, 2013). This definition has provided an opportunity for an early detection of the diseases and other comorbid conditions related to AD-like depression. Evidence shows that early detection in treatment of any disease, medical or psychiatric has a chance for a better outcome for patients. Consequently, early recognition and treatment has an enormous impact on patients' well-being and is cost effective. Therefore, recognizing and treating depression in order to maximize function appears to be an important step.

The purpose of this independent study is to increase the knowledge of Advanced Practice Psychiatric Nurses (APPNs) surrounding treatment of depression in patients with AD, and therefore increasing the quality of care available to the population of interest. The goal of this paper is to identify key terms and definitions related to depression in individuals with Alzheimer's disease, describe methodology in psychiatric assessment, synthesize existing evidence-based best practice in non-pharmacological and pharmacological treatment, and

address interdisciplinary care. Supplied with the most current knowledge related to treatment of depression in people with Alzheimer's disease, APPNs can be well-appointed to provide a comprehensive care for this rising population.

Significance

The available data suggest that the incidence of depression in patients with Alzheimer's disease is high, though there has not been a definite increase in efficacy of treatment for individuals in this population seeking care over the past two decades. This situation causes increase in demand for care, coupled with the increasing need for psychiatric providers, and suggests that APPNs will be required to provide care for depression in patients suffering from Alzheimer's disease at some time in the course of their professions. Furthermore, evidence shows that the incidence of serious psychiatric comorbidity is high among AD patients, indicating that these patients may initially present for care of another mental or medical issue (Mussele at al., 2012). It is crucial that every APPN have the capability to provide assessment, treatment and applicable referrals for this vulnerable population.

Patients with depression in Alzheimer's disease, their families and caregivers face many challenges in their lives, and are in need of mental health professionals who are knowledgeable and able to provide care according to the highest and most current standards of care. Depression in AD patients may not have been diagnosed and treated because of overlap of symptoms of depression and AD. Thompson et al. (2007) showed that treatment of depression, in population of interest, may not be effective in all individuals. Additionally, depression in AD can be organic in nature due to structural changes in the brain or a result of inflammation in the brain and because of that not respond to mainstream treatment of depression (Teper & O'Brien, 2008).

Psychiatric nurses have provided care for geriatric populations for decades, they have managed to deliver high quality care and education. The Standards of Practice for Psychiatric Mental Health Nursing state that the psychiatric nurse "incorporates knowledge of pharmacological, biological and complementary interventions with applied clinical skills to restore the healthcare consumer's health and prevent further disability" (American Nurses Association, 2014, p.59). APPNs definitely need to follow this standard of care and provide comprehensive psychiatric care to the population of interest. At the same time, APPNs need to integrate "ethical provisions in all areas of practice" (American Nurses Association, 2014, p.67) when it comes to applying nursing process in treatment of patients with depression in AD.

Theoretical Framework

Lenz and colleagues' Theory of Unpleasant Symptoms provides an excellent framework from which to view pharmacological and non-pharmacological treatment of depression in AD patients. Lenz and Paugh (2008) explained the purpose of their theory stating that this theory can "improve understanding of the symptoms experience in various context and provide information useful for designing effective means to prevent, ameliorate, or manage unpleasant symptoms and their negative effects" (p.160). Lenz, Pugh, Milligan, Gift and Suppe (1997) described three major components of the theory. First, the theory recognizes the symptoms that the individual is experiencing like psychomotor retardation, emotional lability, weight loss or insomnia in Alzheimer's patients suffering from depression (Lee & Lyketsos, 2003). Secondly, the theory acknowledges influencing factors that cause or affect the symptoms of depression which are influenced by neuropathological changes by Alzheimer's disease by itself (Aznar & Knudsen, 2011).Finally, the theoretical framework noticed the consequence of symptom experience like

decrease in cognitive function among patients suffering from depression in AD (Di Iulio et al., 2010).

The Theory of Unpleasant Symptoms helps APPNs to recognize the need to assess multiple aspects of symptoms and treatment based on duration, intensity, quality and distress. APPNs are able to evaluate performance of pharmacological or non-pharmacological treatment in terms of symptoms influencing cognitive functioning, functional status, or physical performance in depression among AD patients (Lenz at el., 1997). Though a thorough exploration of symptoms of depression in AD patients is beyond the scope of this paper, it is important to notice that there is no clear distinction between symptoms of Alzheimer's disease and depression in Alzheimer's disease (Lee & Lyketsos, 2003). It is the obligation of APPNs to remain educated about the best treatment options for depression in patients diagnosed also with AD to promote the best health outcomes for patients, their families and caregivers.

Definitions

Acetylcholinesterase- is the primary cholinesterase in the body, it works as an enzyme that catalyzes the breakdown of acetylcholine and other choline esters that function as neurotransmitters; it stops the signal between a nerve cell and a muscle cell

Alzheimer's disease – an irreversible, progressive brain disease that gradually destroys memory and cognitive skills, and finally the ability to carry out the most basic tasks

Antidepressants- represent a broad group of drugs that are used in the treatment of depression; this class of medications includes Selective serotonin reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs), Tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOIs) and atypical agents

Antipsychotics- are a class of drugs used to treat symptoms of psychosis and other psychiatric conditions

Dementia- old term used to describe a chronic group of symptoms related to loss of memory and other cognitive functions, the word was replaced by the neurocognitive disorders term

Depression- a mental health disorder described by persistently depressed mood, or loss of interest in activities and causing significant impairment in daily life

Mood stabilizers- is a medication used to treat mood disorders characterized by significant mood shifts

Neurocognitive disorders- are characterized by decline in one or more cognitive areas like memory, attention, language, learning, perception and social skills

Non-pharmacological treatment- is a treatment aimed at management of symptoms of a disease or condition which does not include pharmaceutical medications use, this treatment may include acupuncture, exercise, light therapy, music therapy and others

Pharmacological treatment- management of condition by utilizing pharmaceutical medications

Literature Review

Treatment of Depression in Patients with Alzheimer's Disease with Antidepressants

Antidepressants remain the main treatment for depression in AD. Orgeta, Tabet, Nilforooshan, and Howard (2017) recently conducted a systemic review and meta-analysis of seven double blind randomized controlled trials (RCTs) of efficacy antidepressants for depression in AD. The selected RTCs compared antidepressant (three studies examine sertraline, one study studied both sertraline and mirtazapine and other studies compared imipramine, fluoxetine and clomipramine) versus placebo for depression in AD. The study failed to display any significant difference between antidepressants and placebo in response to treatment.

Similarly, a meta–analysis by Sepehry, Lee, Hsiung, Beattie and Jacova (2012) failed to show superiority of selective serotonin reuptake inhibitors (SSRIs) like serotonin fluoxetine, citalopram, escitalopram and paroxetine versus placebo treatment. A narrative review of Farina, Morell and Banerjee (2017) brought the same results when it examined 36 randomized controlled trials which included newer drugs like mirtazapine, a noradrenergic and specific serotonergic antidepressant. Farina, Morell and Banerjee (2017) pointed out that individuals recruited for trials examining selective serotonin reuptake inhibitors (SSRIs) and or serotonin-noradrenaline reuptake inhibitors (SNRI) displayed reduction of depressive symptoms. Nevertheless, the same level of change was seen in the placebo group thus these improvement in symptoms in depression cannot be attributed to the antidepressants.

Furthermore, Nelson and Devanand (2011) published a systematic review and meta-analysis of seven (n=330) randomized placebo-controlled trials to investigate the effectiveness of antidepressants (imipramine, clomipramine, sertraline, venlafaxine and fluoxetine) in dementia. The findings showed that depressed people with dementia treated with antidepressant compared with the placebo controls had greater odds of experiencing clinically significant improvement. However, the odds ratio (OR) was 2.12 and 95% confidence interval (CI) 0.95-4.70; so neither of these results were statistically significant. Thompson, Herrmann, Rapoport and Lanctot (2007) found antidepressants to be superior and statistically significant compared with the placebo controls (OR 2.32 and 95% of CI 1.04-5.16) in their meta-analysis. The authors also established that individuals taking antidepressants had greater odds (OR 2.75, 95% CI 1.13-6.65) to achieve remission of their depressive episode. The study did not compare antidepressant classes but separate antidepressants (imipramine, clomipramine, sertraline and fluoxetine), the selected RTCs were small (the five studies involved a total of 82 individuals treated with antidepressants

and 83 individuals who received placebo treatment), the researchers used DSM-III and DSM-IV for criterion of depression diagnosis.

Orteg et al. (2017) noticed that most of the studies used a not validated tool for use in patients with AD, Hamilton Depression Rating Scale for Depression (HDRS) and only two RCTs used Cornell Scale for Depression in Dementia (CSDD). The CSDD was developed for assessing depressive symptoms in patients with dementia and remains a gold standard of assessment of depression in AD clients (Alexopoulos, Abrams, Young & Shamoian, 1988). Sepehry at al. (2012) also reported in their meta-analysis use of both CSDD and HDRS as a guide to evaluate recovery. Additionally to HDRS and CSDD, Farina, Morell and Banerjee (2017) reported that their RTCs also used the Montgomery-Asberg Depression Rating Scale (MADRS), The Geriatric Depression Scale (GDS) and the Neuropsychiatric Inventory (NPI) to assess and evaluate symptoms of depression in AD which have their limitations in population with dementia (Korner et al., 2006). NPI was also used in study by Prosteinsson et al. (2014).

Prosteinsson et al. (2014) conducted a multicenter, retrospective, randomized, double blind, placebo controlled, parallel group study of 186 individuals, called the Citalopram on Agitation in Alzheimer's Disease Study (CitAD). The participants of the trial were randomized, received a psychosocial intervention and either placebo (n=92) or psychosocial intervention and citalopram (n= 94) for 9 weeks. The mean age of subjects was in their 70's, 46 percent were women, 66 percent were white and non-Hispanic and they were diagnosed with dementia for 5 years. The authors started participant at 10 mg daily and planned to titrate to the goal of 30 mg daily. The purpose of the study was to assess the efficacy of the antidepressant for agitation among patients with AD but without major depressive disorder, by the use of the following measurements: Neurobehavioral Rating Scale subscale, modified Alzheimer Disease

Cooperative Study-Clinical Global Impression of Change scale, and NPI. CitAD reported positive outcomes for citalopram when compared with placebo on agitation. A following secondary analysis (Leonpacher et al., 2014) evaluated the effect of citalopram on neuropsychiatric symptoms in AD. Leonpacher et al. (2014) found a statistically significant result of the drug on specific NPI domains like delusions, anxiety and arability nonetheless not on depression or dysphoria (OR 0.63, 95% CI 0.34-1.39).

The authors of the CitAD study had to change their protocol regarding dosages of citalopram because during the trial the Food and Drug Administration (FDA) issued an advisory warning that citalopram can prolong QT-interval and advised not to use more than 20 mg of the drug daily in the elderly (FDA, 2011). These findings are very essential to consider when prescribing citalopram for AD clients when the main symptom of depression could be agitation. Particularly, since Prosteinsson et al. (2014) found that citalopram not only increases the risk for averse cardiac events but also slightly reduces cognition. Conversely, Ortega et al. (2017) found no negative effect of antidepressants on cognition and reported increased adverse effects in the antidepressant group but no significant differences when compared with the placebo group. Furthermore, Mokhebr et al. (2014) reported in their study, patients who received sertraline reported most frequently headache and restlessness; clients who took venlafaxine reported most often nausea and restlessness, and desipramine group reported drowsiness and dry mouth as a frequent side effect. The authors stated that the severity of side effects was low in the study but did not offer statistical data. Sepehry at al. (2012) noticed that fluoxetine was better tolerated than sertraline in their study. Escitalopram was also well tolerated among subjects of interest (An et al. 2017). De Picker, Van Den Eede, Dumon, Moorkens and Sabbe (2014) reported a moderate risk of hyponatremia in AD patients treated with SSRIs, mirtazapine and venlafaxine.

A retrospective quantitative research, included data from multiple countries (Australia, Canada, United States of America, United Kingdom, France, Germany and Spain), found no statistical association of hemorrhage for commonly prescribed SSRIs and non-SSRIs among general population (Gahr et al., 2015). Some of the studies did not report any data about tolerability of antidepressant (Farina, Morell & Banerjee, 2017; Orgeta, Tabet, Nilforooshan & Howard, 2017).

An et al. (2017) currently conducted a retrospective twelve weeks randomized, double blind, placebo controlled trial with open-label, with a twelve week extension period study in South Korea, which was not included in any of the discussed meta- analysis above. The study examined the efficacy of escitalopram, the S-enantiomer of citalopram (Stahl, 2013), SSRI, on symptoms of depression (mood and cognition) in individuals diagnosed with AD. The study included 84 subjects (50 years or older) randomized into two even groups: treatment or placebo. Though, 29 percent of subjects did not finish the study. Demographics and baseline clinical characteristics were similar between groups but 80 percent of subjects were females. The study group received 5mg a day of escitalopram, the dose was increased 5 mg a day every two weeks for the maximum-target total of 15 mg of escitalopram. To measure the effectiveness of antidepressant the severity of depression in subjects was assessed using CSDD and Geriatric Depression Scale (GDS) every 4 weeks.

An et al. (2017) found no significant difference between the treatment and placebo group in improving depressive symptoms in individuals with AD. The study had multiple limitations: the drop-out rate was high causing a small study group, researchers used Olin's criteria for depression in AD and not DSM –V, the subjects were mainly women and all individuals were of Korean ethnicity. The findings cannot be generalized to the general population in North America because of its obvious limitations. There are not available, in English literature, studies of

escitalopram in North America or Europe in the last 10 years. Hence, more research is needed to examine the topic which would include more subjects and thus more statistical power.

None of the previous meta-analyses included the results of a small, retrospective twelve weeks RTC done by Mokhber et al. (2014). The study compared sertraline, venlafaxine and desipramine in 59 individuals (25 women and 34 men) and examined the effect of the antidepressants on depression, cognition and the daily living activities in AD patients in Iran. All the subjects in the study had a diagnosis of AD supported by neuro-imaging and a diagnosis of major depressive disorder (MDD) diagnosed using DSM-IV. To evaluate MDD the authors used HRSD which was administered at the beginning of the trial and at 2, 4, 8, and 12 weeks.

The study found that only individuals treated with sertraline revealed a significant decline in the scores of the Hamilton Depression Rating Scale compared with baseline ($p < 0.05$). Desipramine improved depression meaningfully after 2 weeks and showed the fastest treatment response among these three medications, however the results were temporary and disappeared after 12 weeks. Moreover, venlafaxine treatment was also temporary, showed treatment response by week four and became insignificant like despiramine treatment by the end of the trial (Mokhber et al., 2014).This RTC had multiple limitations. The sample size was small and the study had no placebo control group. In addition, Mokhber et al. (2014) used a non-validated rating scale in this population of interest and did not report side effects of the drugs. The study was conducted only among an Iranian sample of subjects and with the limitations mentioned above, it is difficult to draw general conclusions from these data and make recommendations.

Multiple meta - analysis and RTCs discussed in length are inconsistent with findings to determine evidence that antidepressants are efficient in treatment of depression in Alzheimer' disease and agreed that there is a need for further, well designed methodologically RTCs with

large samples to confirm the therapeutic effect of antidepressants in AD (Nelson & Devanand, 2011; Orgeta, Tabet, Nilforooshan & Howard, 2017; Sepehry, Lee, Hsiung, Beattie & Jacova, 2012; Thompson, Herrmann, Rapoport & Lanctot, 2007).

There continues to be mixed evidence for the efficacy of antidepressants in treatment of depression in Alzheimer's disease. Therefore, the American Association for Geriatric Psychiatry (2006) recommends a therapeutic trial with antidepressants only in difficult cases (ASGP, 2006). On the other hand, the American Psychiatric Association Practice Guidelines (2007) recommendations are based on the side-effect profile of antidepressant and individualized characteristics of the patients. APA utilizes a coding system of their recommendations from I to III using Roman numbers, the three classes represent levels of confidence. Level I (substantial clinical confidence) endorses use of SSRIs since they are better tolerated than other antidepressant medications. At the same time drugs with substantial anticholinergic effects like amitriptyline and imipramine should be avoided. Level II (moderate clinical confidence) recommends use of bupropion, venlafaxine and mirtazapine. APA also recognizes use of electroconvulsive therapy (ECT) based on the clinical experience despite lack of research related to the topic. Level III (based on individual characteristics) recommends careful use psychostimulants (APA, 2007). The Canadian Medical Association Journal (2008) published a statement supporting use of SSRIs because of their small anticholinergic activity.

Treatment of Depression in Patients with Alzheimer's Disease with Other Drug Classes

Acetyl cholinesterase inhibitor and memantine are recommended for treatment of AD, but their effect on depression is not well established (Briks, Chong, Grimley & Evans, 2015). Rodda, Morgan and Walker (2009) conducted a systematic review of 14 RTCs to examine the efficacy of donepezil (9 RTCs), rivastigmine (2 RTCs), and galantamine (3 RTCs) in the

treatment of behavioral and psychological symptoms of Alzheimer's disease. The study found a clinically modest but statistically significant effect of the drugs compared with placebo in three trials. However, depression scores were not reported separately, many of RTCs had methodological limitations like low NPI scores at baseline and behavioral and psychological symptoms of dementia (BPSD) as secondary results. On the other hand, Schmidt et al (2010) investigated the effect of memantine on behavioral symptoms in a 16-week, prospective, naturalistic open-label study of 53 patients with AD. The authors used NPI as a main measurement scale. The study reported a 4.6-point improvement on the total NPI scores ($p < 0.01$) with the key benefits seen in depression (-24.6%) and aberrant motor behavior (-16.9%). This study gave promising results but placebo-controlled trials are needed to consider any recommendation regarding memantine ant treatment of depression in AD. However, a following systematic review and meta- analysis by Lockhart, Orme, and Mitchell (2011) of two RTCs failed to show a benefit of memantine on behavioral symptoms versus placebo (95% CI – 4.78, 1.49). Hence, current available research does not support the use of memenatine or cholinesterase inhibitors to treat symptoms of depression in AD.

Antipsychotic medications are used to treat BPSD. The evidence shows modest benefits and a possibility of serious side effects and increased stroke and mortality rate (Tampi, Tampi, Balachandran & Srinivasan, 2016). The Clinical Antipsychotic Trials of Intervention Effectiveness- Alzheimer's Disease (CATIE-AD) was done eleven years ago and compared olanzapine, quetiapine, and risperidone and compared with placebo on aggression, agitation and psychosis over 36 weeks. First, the efficacy of the principal outcome showed advantages of olanzapine and risperidone but not quetiapine ($p = 0.002$). The medications were poorly tolerated in the treatment groups ($p = 0.009$) (Schneider et al., 2006). This study was followed by a later

analysis of the effect of treatment on particular symptoms and showed that subjects in the trial in the olanzapine group experienced a worsening of the "withdrawn depression" element of the Brief Psychiatric Rating Scale. The treatment factors were the same as placebo groups on the CSDD since all the p values were more than 0.5 (Sultzer et al., 2008). The use of antipsychotics to manage depression cannot be justified since there is lack of data addressing particularly the role of antipsychotics in treating depression in AD and proven potential risks over benefits.

Very few studies have examined the use of mood stabilizers as a treatment of depressive symptoms in AD. Lithium has been suggested as a potential therapeutic or preventive medication in Alzheimer's disease because of its function in the phosphorylation of the tau protein (Kessing, Forman & Anderson, 2010). Hampel et al. (2009) designed a retrospective RCT which was single blind, placebo-controlled and lasted 10 weeks. The study involved 71 patients (38 placebo treatment and 33 lithium treatment) with mild AD with MMSE (scores 21-26). The trial had 6 weeks titration phase and the goal of lithium level was 0.5-0.8 mmol/L. The RCT did not show any improvement in markers of tau protein or cognitive function, neuropsychiatric measures including depressive symptoms. Another, recent meta-analysis looked at lithium as a treatment for AD and found that lithium significantly decreases cognitive decline as compared to placebo. Nevertheless, the study did not measure or discuss the influence of lithium on symptoms of depression in AD (Matsunaga et al., 2015).Furthermore, Sodium valproate is used to treat behavioral symptoms in dementia. Cochrane review by Lonergan and Luxenberg (2009) did not support treatment of aggression with valproate preparation and pointed to multiple side effects like falls, infections and gastrointestinal diseases. Lamotrigine has been found to be an effective mood stabilizer in bipolar depression (Stahl, 2013). Suzuki and Gen (2015) investigated in a retrospective small open-label study (40 participants), naturalistic observational trial of AD

patients who needed a change in medication because of symptoms not responding to treatment or problematic side effects. The individuals were divided in two groups, twenty patients each in every group. One group included the individuals who were taking psychotropic medications at the entry level and then switched to lamotrigine for 16 weeks, the other group sustained on other psychotropic medications. Subjects in the treatment group showed a statistically significant improvement in their NPI score ($p<0.005$) but not on the depression score ($p<0.005$); no significant difference was seen when the groups were compared to each other. The study had multiple limitations. It was a short- term study, the sample was small and the study was designed as open-label rather than double-blind study.

Some studies examined the efficacy of non-psychotropic agents on symptoms of depression on AD patients. Valen – Sendstad et al. (2010) conducted a retrospective, randomized, double-blind, placebo-controlled study of a low-dose of estradiol and norethisterone. The study's goal was to examine the effects of the hormone therapy on cognition, activity of daily living and depressive symptoms in women with AD. Sixty-five females, aged 65-89, met criteria of probable AD according to DSM-IV and were randomly assigned to take either 1mg of estradiol and 0.5 mg of norethisterone or placebo once daily for twelve months. The primary outcomes were measured on the Consortium to Establish a Registry for AD (CERAD). A noteworthy treatment effect for depressive symptoms was observed in the hormone group therapy in CERAD depression screen ($p<0.0052$). Additionally, a linear model analysis showed a significant effect on mood. It is relevant to notice that forty five percent of the patients receiving medications experienced one or more adverse effects, for a total of 25 adverse effects (20 mild and 5 moderate) in the treatment group. On the other hand, the placebo group reported thirty eight percent of adverse events, for a total of 18 adverse effects and 12 of them were mild.

The used combination of hormone therapy is common in Europe but not in the United States. The study included a small sample of participants. The role of hormone therapy in improvement of depressive symptoms in AD is controversial and there is not any other research examining the role of hormone replacement therapy in depression in AD individuals in the last 10 years to compare. Hence, no recommendations can be concluded from this single study but a need for further research related to this topic. The authors concluded that hormone therapy interacts with the apolipoprotein E (ApoE) genotype in women with AD and better results in mood and cognition were seen in treatment group when women did not have ApoE 4 allele (Valen – Sendstad et al., 2010). On the other hand, Fred- Levi at al. (2008) researched the effect of dietary omega-3 supplementation on psychiatric and behavioral symptoms in AD, daily function in relation to ApoE genotype. The retrospective, randomized, double-blind and placebo-controlled study included 204 subjects with AD from 65 to 83 years old who met criteria of mild to moderate AD using DSM-IV. Psychiatric symptoms were measured with NPI and MADRS. The RTC showed found significant positive treatment effects on the NPI agitation domain in ApoE 4 allele carriers ($p = 0.006$) and also MADRS scores non- ApoE 4 allele carriers. This is the only RTC ever done researching the topic of interest and more research is needed to draw any recommendations.

Non-pharmacological Treatment of Depression in Patients with Alzheimer's Disease

Treatment with antidepressants and other class medications has not shown significant effect on depression in people with AD. Therefore, it is important to examine and consider non-pharmacological treatments for depression in AD. Electroconvulsive therapy (ECT) is one of the promising nonpharmacological treatments for older adults over 65 years with dementia (Oudman, 2012). However, there are no studies available which would examine the efficacy and

safety of ECT when it comes particularly to depressed patients with AD. Narita and Yokoi (2017) are currently designing an RTC to examine transcranial direct current stimulation (tDCS) for depression in AD. The study is at the stage of recruiting subjects for the trial. While tDCS shows promising effect among younger adults it was never studied in AD patients. This trial could bring some important insight into treatment of depression in AD.

Exercise has been shown to be an effective tool for reducing depressive symptoms in general population. Williams and Tappen (2008) designed an RCT, to examine routine exercise like supervised walking and social conversation on depression in AD patients living at nursing homes. The subjects in the study were randomly divided into three treatments groups and followed a 16-week long trial with interventions five times a week for thirty minutes. The first experimental group (n = 16) followed comprehensive individual walking which included ten minutes of balance, strength and flexibility exercise and then twenty minutes walking program. The second experimental group (n = 17) followed supervised individual walking for 30 minutes. The subjects could take breaks if they wished and use assistive devices, the interventionists walked by the subjects and used gait belt for assistance. The third group (n = 12) was a control group and individuals assigned to this group had casual conversations for thirty minutes. Therapeutically oriented conversations like life review and reminiscence therapy were prohibited. The participants of the study ranged from 71 to 101 years with the mean being at 87.9, eighty percent were European Americans and twenty percent were Hispanic. Symptoms of depression were measured by CSDD. The subjects were included in the trial with a score of 7 or above. The mood was assessed using the Dementia Mood Assessment Scale (DMAS) and Alzheimer's Mood Scale and affect was scored on the Observed Affect Scale (OAS). The scores for CSDD dropped in three groups and 16 participants had CSDD scored under 7, however p

value was not reported. On the other hand, DMAS outcome ($p = 0.0003$) and OAS scores ($p < 0.001$) showed to be statistically significant. The authors reported that the exercise groups had better outcomes than the conversation group but statistical data are unavailable. The authors did not publish separate outcome scores for every group but provided only scores for three groups together. The samples were small and data about gender of participants was not provided. Almost forty percent of individuals were receiving antidepressants and these variables were not controlled during the study. On the other hand, a systematic review looked at how physical exercise impacts quality of life of people with depression and Alzheimer's disease (Tavares, Moraes, Deslandes & Laks, 2014). The study considered six RCTs. The study found improvement in depression using the Short Form Health Survey (SF-36) which is not specific to evaluate depression in AD and it also reported improvement in all domains besides general health. The included RCTs used different exercise types (aerobic, balance, strength and flexibility) and so no recommendations could be drawn about intensity, duration and type of exercise to improve depression in AD patients. Still, the authors concluded physical exercise can add in treatment of depression. The samples in all RCTs were small and differed in duration (from 8 weeks to 24 months).

Many studies have examined the effect of music therapy (MT) in management of depression in dementia patients but research which studies the effect of music therapy in individuals suffering particularly from Alzheimer's disease and depression is limited. Guetin et al. (2009) conducted a retrospective, 18 months long with a 6-month follow-up period; randomized, controlled study to examine the effect of MT on depression and anxiety in patients with AD. The treatment group included 15 subjects and they took part in weekly sessions of individualized, receptive MT. The individuals chose their own musical style. The control group

had also 15 participants and they participated in weekly reading sessions. Patient's level of anxiety was scored on the Hamilton Scale and depression on the GDS. The authors reported a significant improvement in both depression ($p<0.01$) and anxiety ($p<0.01$) from week 4 to week 16 in the treatment group when compared with the control group. The study showed that the effect of MT was sustained for up to 8 weeks after the therapy was discontinued between weeks 16 and 24 ($p<0.01$). The participants in the study had mild to moderate AD but the research did not specify the kind of depression the participants suffered from. The researchers did not include any information about medications for treatment of depression in the subjects and this variable was not considered. The sample was small and the results were evaluated under blind condition but the subjects and the interventionists were not blinded. Most of the participants were female (73 percent) in their 80's, mostly widowed or divorced, the study did not consider the ethnical background of the subjects. The recent study brought similar results. Orti et al. (2017) designed an analytical, quasi-experimental, retrospective study which included 25 participants. The subjects in the study were from 71 to 86 years old with MMSE scores ranging from 18 to 23. The female subjects were represented in majority (above 77 percent) over male subjects (less than 23 percent). The participants received MT in 60-minute therapy weekly. First, the welcome song was played and then songs with lyrics relating to flowers. Interestingly, patients' saliva was collected to measure the level of salivary cortisol using the Enzyme-Linked Immuno Sorbent Assay (ELISA) before and after MT. The subjects completed Hospital Anxiety and Depression Scale (HADS) to measure anxiety and depression. The study showed that levels of the cortisol decreased after music therapy. The authors reported that decrease in cortisol decreased scores on HADS when it comes to depression but not anxiety. The study showed promising results with MT in depressed patients with AD. However, the study had a small sample, it did not have a

control group, patients' medications were not included as a variable and the study used an invalid scale to measure depression in AD patients.

Dowling, Graft, Hubbard and Luxenberg (2007) researched the efficacy of bright light therapy for sleep disorders and agitated behaviors in AD patients in their retrospective RCT which lasted 11 weeks. This study compared two experimental groups which were randomly assigned and exposed to morning (n=29) or afternoon (n=24) bright light therapy to a control group (n=17) which received only usual indoor light levels. The subjects were recruited from two long-term care facilities in California and had diagnoses of AD and experienced insomnia, frequent awakening during nighttime, wandering at night or extensive sleepiness during daytime. Individuals were excluded if they had any other form of dementia like Parkinson's disorder, stroke or were taking sleeping aids. Participants included 57 women and 13 men from 59 to 98 years old, mostly Caucasians. The primary outcome was measured using the Neuropsychiatric Inventory-Nursing Home (NPI-NH). The analysis of results showed that the bright light therapy in the morning improved NPI-NH aberrant motor behavior score ($p<0.007$). Though, this treatment was also linked to a significant increase on the NPI-NH agitation/aggression subscale when compared to baseline ($p = 0.009$). This study also has multiple possible limitations and biases. In this RCT, the certified nursing assistants (CNAs) who were most familiar with the residents were assigned to the subjects in the study and filled out the ratings. The study had a small sample of participants and changes in medications of participants in the 11-week study were not considered when examining results. There are more recent studies examining the effect of light therapy on depression in dementia but not particularly in AD.

Furthermore, Niu, Tan, Guan, Zhang and Wang (2010) designed a retrospective RCT to study cognitive stimulation therapy in the treatment and improvement of verbal fluency,

orientation, episodic memory and cognitive impairment. The study took place in a military sanatorium in China and included 32 patients with mild to moderate AD who exhibited neuropsychiatric symptoms described above. The subjects were randomly assigned to a control group (n=16) or a treatment group (n=16) and studied over 10 weeks of clinical trial. All individuals had been taking donepezil (from 5 to 10 mg daily) for at least three months. Two subjects withdrew from the treatment group and one from the control group. The primary outcome was evaluated by the NPI. Individuals compared to control had significant improvement on the NPI ($p< 0.001$); NPI areas of apathy ($p=0.017$) and depression ($p=0.047$). The authors concluded that cognitive stimulation therapy has significant effectiveness in lowering apathy and depression symptoms in patients with AD. The RCT sample was small, and it did not inform about demographic data of participants. There are other studies available examining cognitive stimulation therapy in dementia but not strictly in AD.

Methods

An online search using the Harley E. French Library of the Health Sciences through the University of North Dakota was conducted to investigate the state of current knowledge regarding pharmacological and non-pharmacological treatment of depression in AD individuals. The Cochrane Library, CINHAL, PubMed, PsychINFO, and Psychiatry Online databases were searched for articles specific to the search term “treatment of depression in Alzheimer’s disease”. Search results were limited to articles published between the years 2007 to 2017 in peer-reviewed, English as published language, and animal studies were excluded. The Cochrane Library search returned one result for systematic reviews, and one result concerning treatment of epilepsy in AD. Psychiatry Online returned 167 results; 118 articles were specific to neuroimaging, pathophysiology or dementia, 27 were commentary, related to phenomena of

depression in caregivers of AD patients or related to non-psychiatric care; leaving 12 reviewable articles.

CINHAL initially returned 184 results; 122 articles were specified to dementia and general geriatric population, 17 were related to neuroimaging and pathophysiology and treatment of AD, 18 were related to prevention of AD or caregiver depression, 6 articles were duplicates from previous Psychiatry search, leaving 21 articles. PsychINFO returned 957 results, 866 were not specific to AD, related to pathophysiology and neuroimaging of AD or commentary, 21 articles studied prevention of depression or AD, 17 results took a look at caregivers, 2 articles researched medications not approved by FDA for use in the USA, 17 articles repeated from the previously described above searches; leaving 34 reviewable articles. PubMed search returned 462 articles, 414 were complementary, related to dementia, geriatric population, pathophysiology of depression and AD, neuroimaging or non-psychiatric treatments, 15 results were related to caregivers of AD individuals, 16 articles were already identified by previous searches of other databases; leaving 11 reviewable articles. In addition to the database literature research, a manual search of references, a manual search of the references in the reviewed articles was undertaken with the same search criteria, resulting in 14 more articles.

In order to increase the current level of knowledge surrounding the pharmacological and non-pharmacological care of depression in patients suffering from AD, the key results of this paper were synthesized into an educational PowerPoint (see Appendix). The presentation will be given to clinical staff at Trinity Health, inpatient psychiatric unit. Reaching out to psychiatric clinical staff can directly influence the level of care for depressed patients with AD and openly increase level of knowledge and comfort of clinical staff taking care of this population.

Results

The described online literature search highlighted a depth of research concerning prevention of depression and AD, depression and burn-out among AD caregivers, depression in stroke and other dementias individuals, pathophysiological and neuroimaging changes in depression and AD, as well as symptomology of depression in AD. Due to the treatment focus of this paper, these studies were not included for review. Multiple reviewed RCTs were included in encompassed systematic reviews or meta-analysis and therefore were not included in the literature review separately. Additionally, two foreign studies were excluded because the FDA does not improve studied medications in the United States.

The twenty four studies included in this review consist of three systematic reviews, five meta-analyses, one narrative review, eleven RTCs, one open label study, one analytical quasi-experimental study and two secondary analyses. Finally, national and international standards of care documents and practice considerations were chosen to provide an overview of evidence-based treatment guidelines for APPN practice.

Discussion and Implication for Nursing

Depression in Alzheimer's disease is a multidimensional problem and it requires a complex approach. Regardless of concerns related to the need for continued research into the pharmacological and non-pharmacological management of depression in AD, recommendations for appropriate evidence-based practice can be made. It is above all most significant that APPNs practice with this population and their families and caregivers with up-to-date knowledge and skills. As evidenced by the literature review, diagnosing depression in AD can be challenging especially in individuals with sensory impairments and different presentations of the disease. The lack of established diagnostic criteria for depression in AD may be also a confusing factor.

Furthermore, there are multiple scales which are used to diagnose depressive symptoms (HRDS, NPI, MADRS, GDS) which have not been validated for use in patients with AD. The only validated scale is the Cornell Scale for Depression in Dementia (CSDD) and it should be used additionally to DSM-V by APPNs to diagnose and monitor progress or regression of depression in AD. No research evidence or agreement exists as to what constitutes a clinically meaningful difference in depressive symptoms between drug and placebo treatment in AD. It is vital to notice that the National Institute for Health and Clinical Excellence requires the difference of at the minimum three points as a criterion for clinically significant change in depression in general population (National Collaborating Center for Mental Health, 2004) and APPNs need to follow this recommendation in lack of other evidence. The need to establish valid diagnostic criteria seems to be essential and provide APPNs with room for future research and education. APPNs have a duty to consider specific tools and training in the implementation of depression screening policy for patients with AD.

The small number of studies and use of different types of antidepressants tested and very limited studies on non-pharmacological treatment of depression in AD, make it challenging to draw conclusions about the effectiveness of pharmacological and non-pharmacological treatments for depression in individuals with AD. There is a need for further well-designed multicenter RTCs which would follow high standards of methodology and reporting, include large samples and a diagnostically homogenous population. The deficiency of evidence base makes it difficult to use available research to inform evidence-based policy about whether antidepressants are effective in treating depression in people with AD. These findings do not mean that people with severe depression should not be treated with antidepressants but APPNs should be diligent and cautious when choosing and prescribing antidepressants for patients with

AD. In the absence of convincing evidence to guide APPNs practice, current guidelines usually recommend a trial of antidepressant treatment in the individual with AD where symptoms are distressing and exceed the threshold for major depression. SSRIs (sertraline most frequently studied in RCTs) would be the more preferred choice because of their side effect profile, general tolerability and cost; tricyclic antidepressants should be avoided because of their anticholinergic activity. The atypical antidepressants like venlafaxine and bupropion have not been well studied in AD. The studies about mirtazapine showed that this drug is no more effective than a placebo. APPNs should always educate the patient, family and caregivers about risks and benefits and the decision about treatment of depression in AD should be a cooperative decision. APPNs, in evaluating benefits of antidepressant management should consider the possibility of improved quality of life and increased functional independence. However, risks like injurious falls, exacerbation of suicidal ideation and cardiac electrical activity and polypharmacy should not be underestimated. Additionally, follow-up monitoring for possible side effects and adverse effects should be taken into consideration. Data supporting alternative pharmacological strategies need further research and these points cannot be recommended in routine clinical care. Considering the unclear relationship between depression and AD, it may appear reasonable for APPNs to consider a more individualized approach to treatment of depression in AD.

APPNs can influence knowledge, beliefs and attitudes toward depression in AD and create implementation of evidence-based culturally competent interventions for people interventions for this population; through their involvement with politics and policy at the community, state, and national levels. Additionally, APPNs have a unique role in education. APPNs role as educators are not only limited to the patients and their family but also other helping profession, also community, and state and federal levels. Alzheimer’s disease paired

with depression brings a huge burden to health care and it is relevant for APPNs to be active in research to bring cure not only to AD but also depression. This approach requires collaboration of other professions, funds for research and lobbying for policy changes to address health disparities in mental health in the population of interest. The review of literature pointed out that research concerning management of depression in AD is complex because of its presentation, depression often is diagnosed before AD diagnosis, different scales and diagnostic tools used by practitioners, polypharmacy of the patients and another comorbid mental disorders. Some studies pointed out also that depression is self-limiting and "treatment" is not always to praise. Non-pharmacological interventions like music therapy, exercise and light therapy are giving some promising hopes in treatment of depression in AD but more well-designed studies (RCTs) are needed to make any recommendations for clinical practice and third party reimbursement.

When providing individualized, holistic care, it is recommended that APPNs be familiar with new research concerning pharmacological and non-pharmacological treatment of depression in AD patients. APPNs should always deliver care in congruence with their professional Code of Ethics and Standards of Practice and make appropriate referrals.

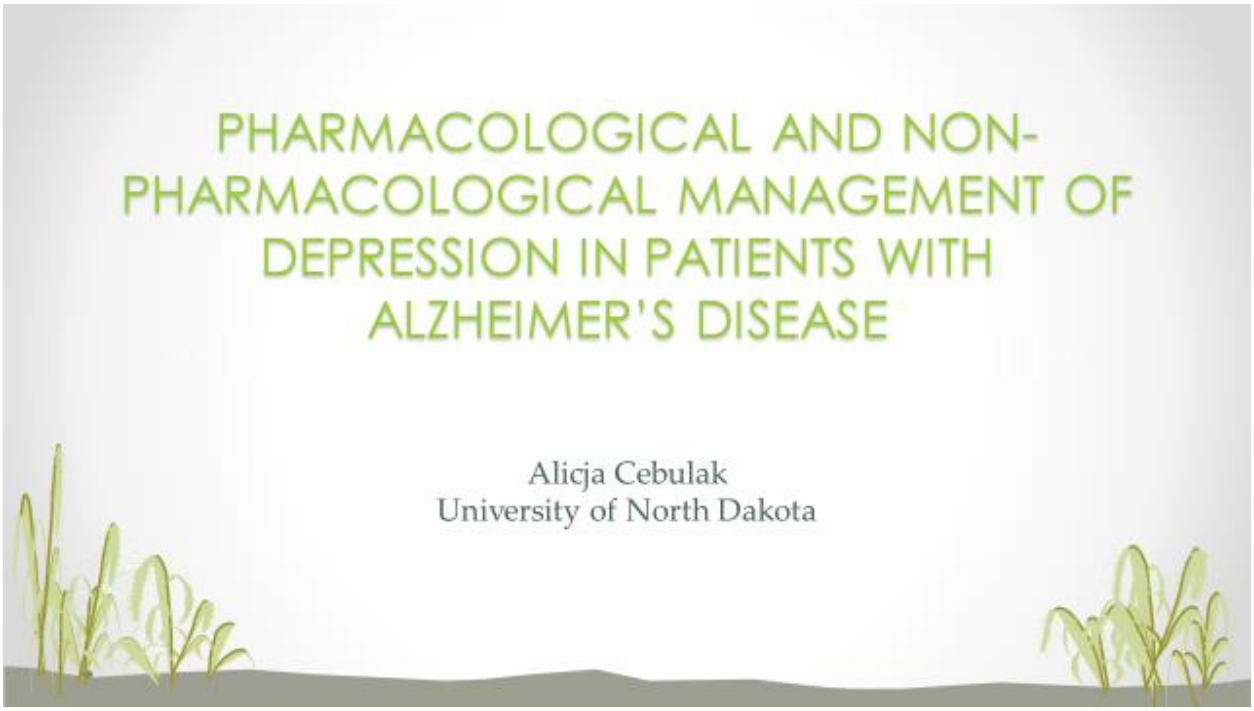
Conclusions

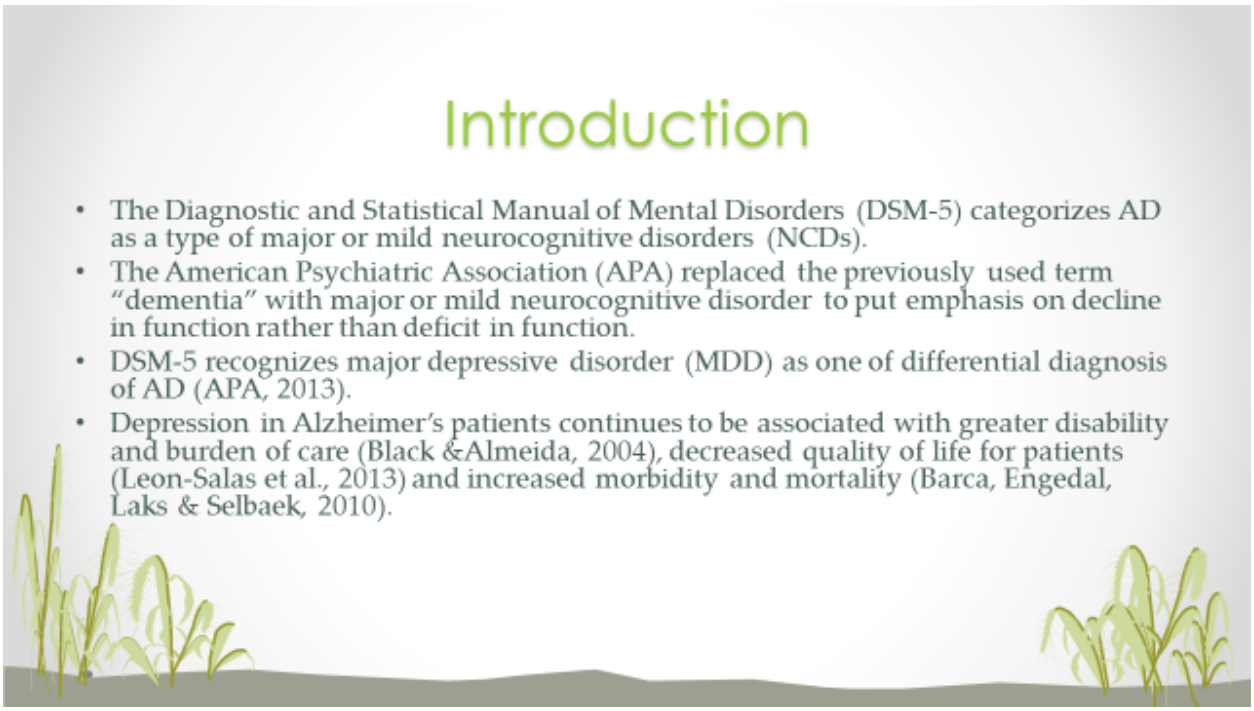
Undoubtedly, the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) has redefined Alzheimer's disease and other types of dementia as minor or major neurocognitive dysfunctions. This approach changed directions of viewing Alzheimer's disease (AD) from a condition characterized by deficit in function to a condition characterized by decline in function. The American Psychiatric Association (APA) started to view AD and other comorbid disorders of AD (like depression) through opportunities of prevention and treatment. Treatment of depression in individuals with Alzheimer's disease is now seen through the lenses of preventing

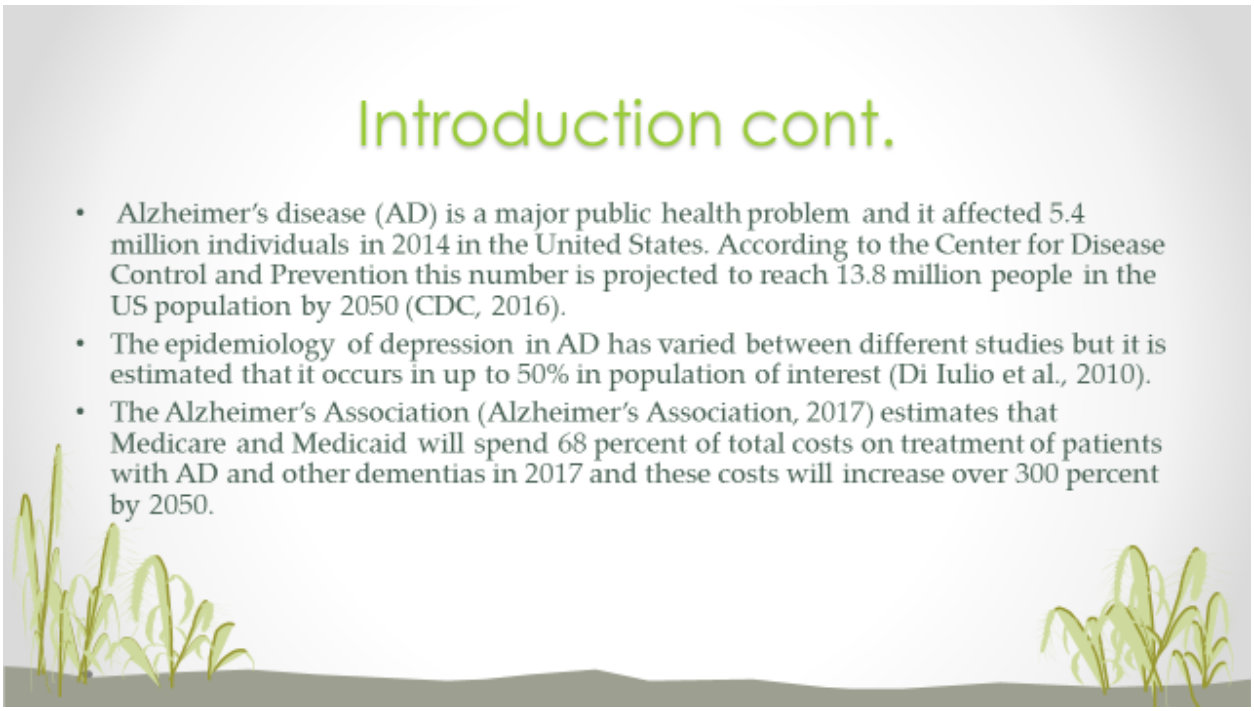
decline in function. Depression is a frequent, comorbid, mental disorder in individuals with Alzheimer's disease. This disorder is commonly associated with an increased risk of morbidity and mortality, an increased utilization of health services, caregiver burnout, and a reduced response to pharmacological and non-pharmacological treatment. Establishing treatment for depressive symptoms in Alzheimer's disease that is both safe and efficacious remains a challenge and an optimal approach to treatment has not been well established. Developing clinical recommendations for the management of depression in this population is an important clinical initiative. Evaluating the role of pharmacological and non-pharmacological treatment in individuals with AD can be also puzzling given the difficulty in recognizing and monitoring the symptoms of depression in AD individuals. Certain symptoms of depression and AD can overlap and be difficult to distinguish. As a result, the consensus on the best scale to use to measure depression in patients with AD has not been well established.

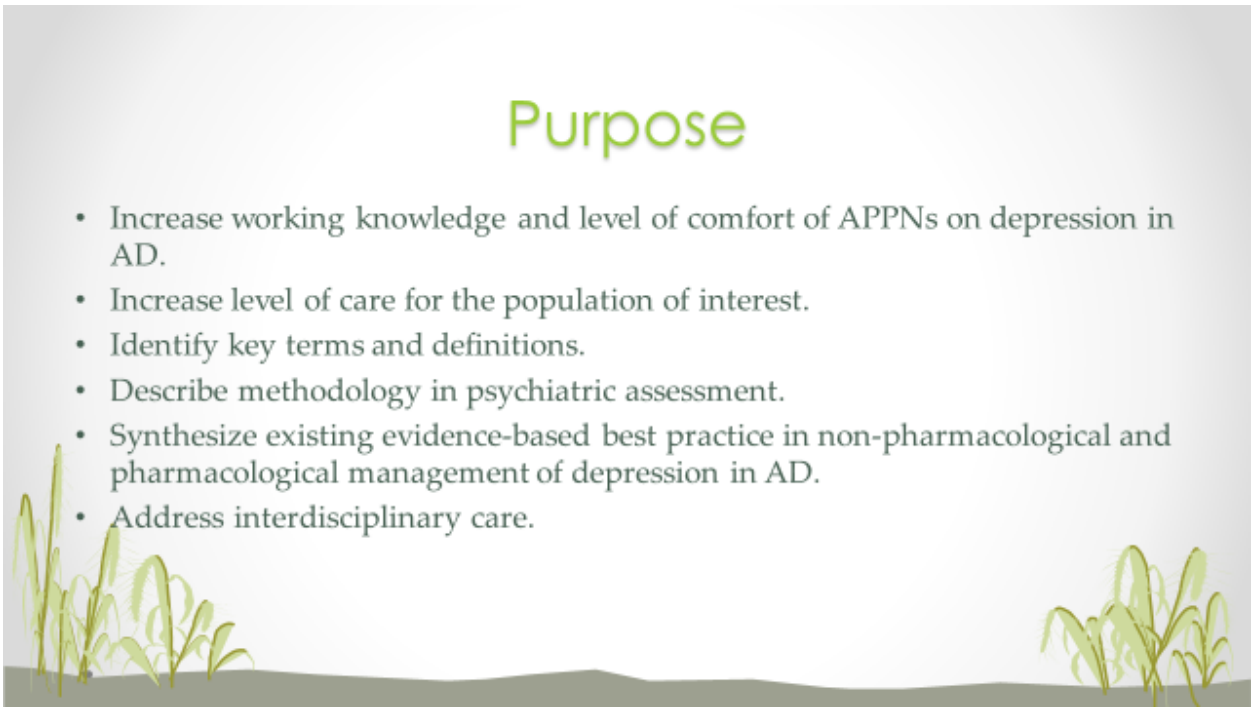
APPNs should screen all patients presenting with AD for depression and deliver best evidence practice, holistic care to his or her patients. This is a new era for APPNs to lead in education, research and change health policy, to be seen and heard. The purpose of this paper has been to widen the education of APPNs on the pharmacological and non-pharmacological management of depression in Alzheimer's disease patients. As health care providers, we have an enormous professional and moral responsibility to our patients and professional organizations to provide comprehensive and effective care.

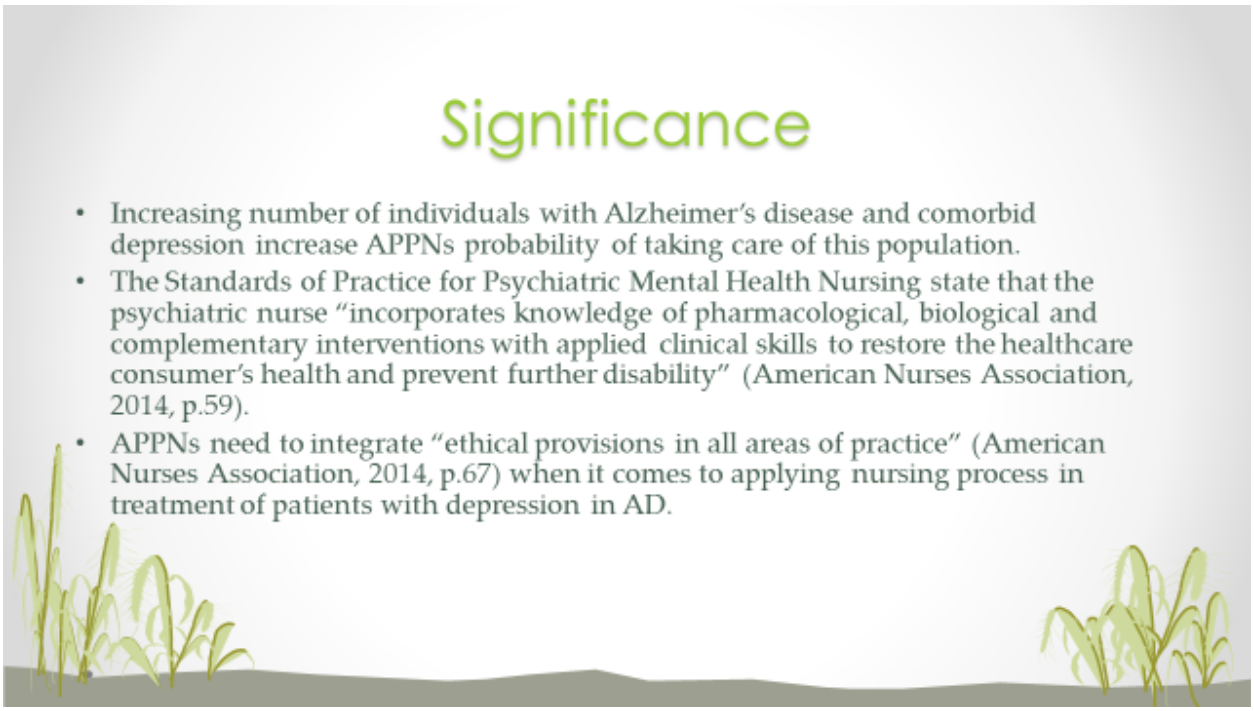
Appendix

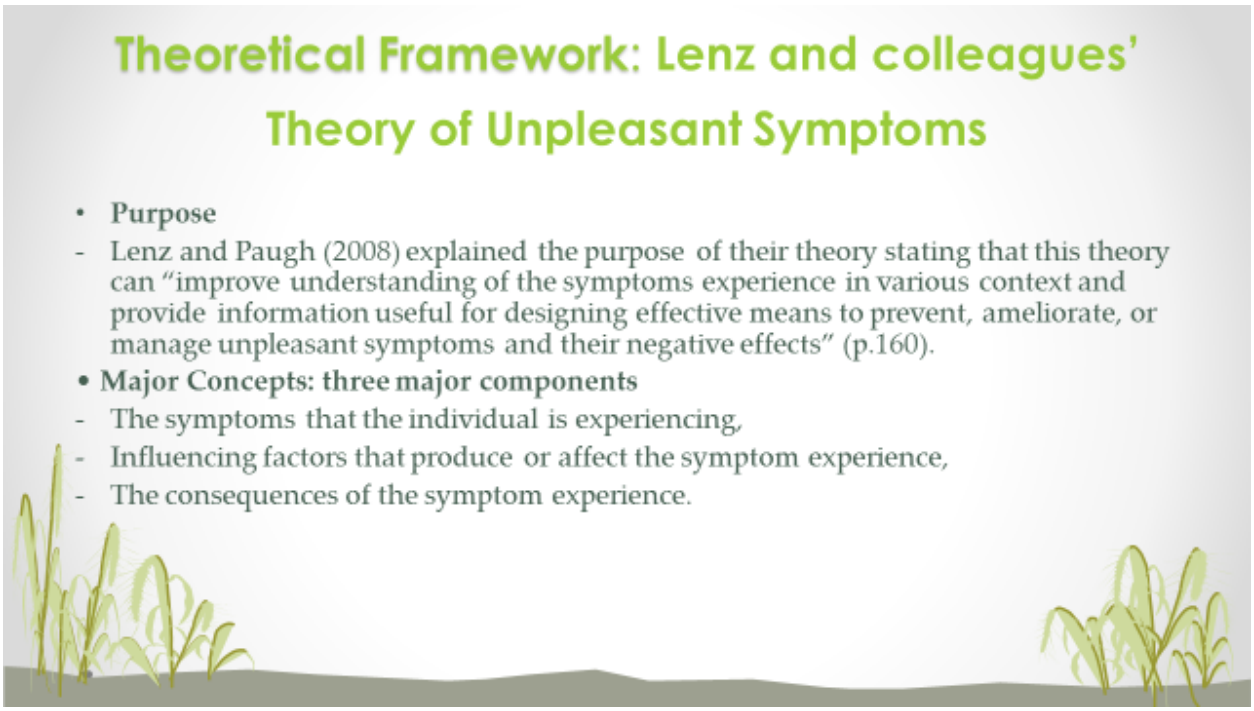

PHARMACOLOGICAL AND NON-PHARMACOLOGICAL MANAGEMENT OF DEPRESSION IN PATIENTS WITH ALZHEIMER'S DISEASE
Alicja Cebulak
University of North Dakota

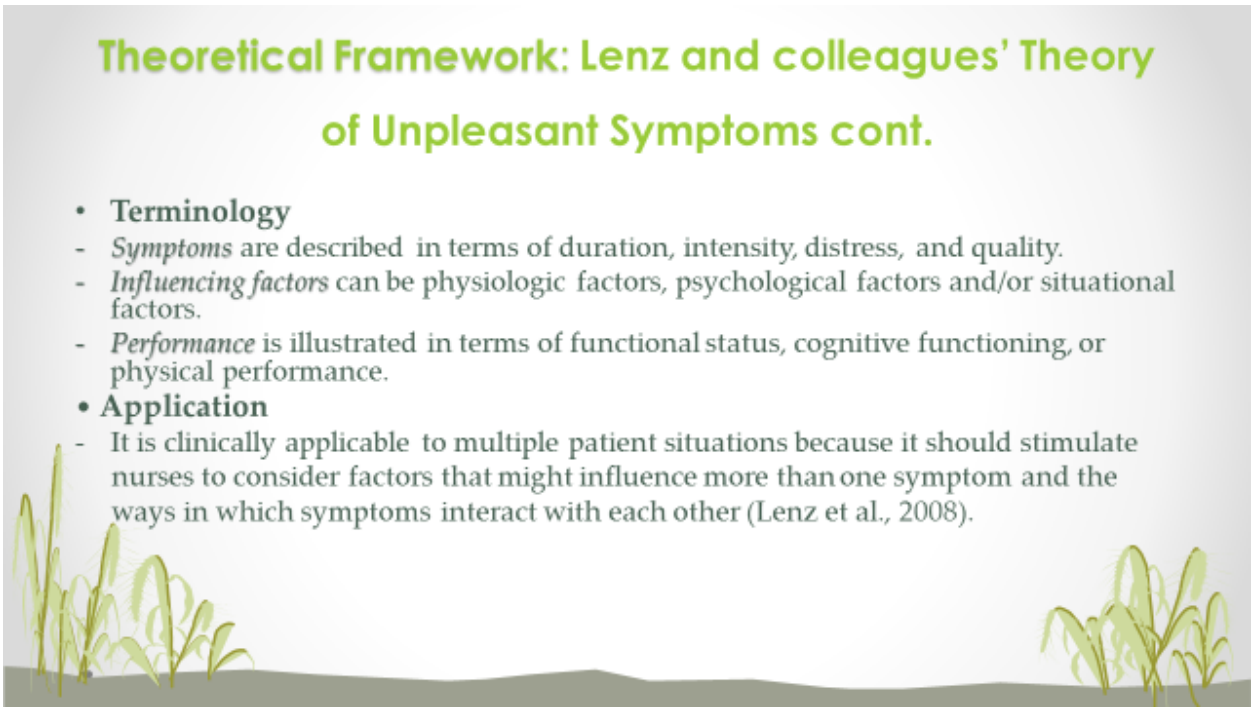

Introduction
The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes AD as a type of major or mild neurocognitive disorders (NCDs).
The American Psychiatric Association (APA) replaced the previously used term "dementia" with major or mild neurocognitive disorder to put emphasis on decline in function rather than deficit in function.
DSM-5 recognizes major depressive disorder (MDD) as one of differential diagnosis of AD (APA, 2013).
Depression in Alzheimer's patients continues to be associated with greater disability and burden of care (Black &Almeida, 2004), decreased quality of life for patients (Leon-Salas et al., 2013) and increased morbidity and mortality (Barca, Engedal, Laks & Selbaek, 2010).

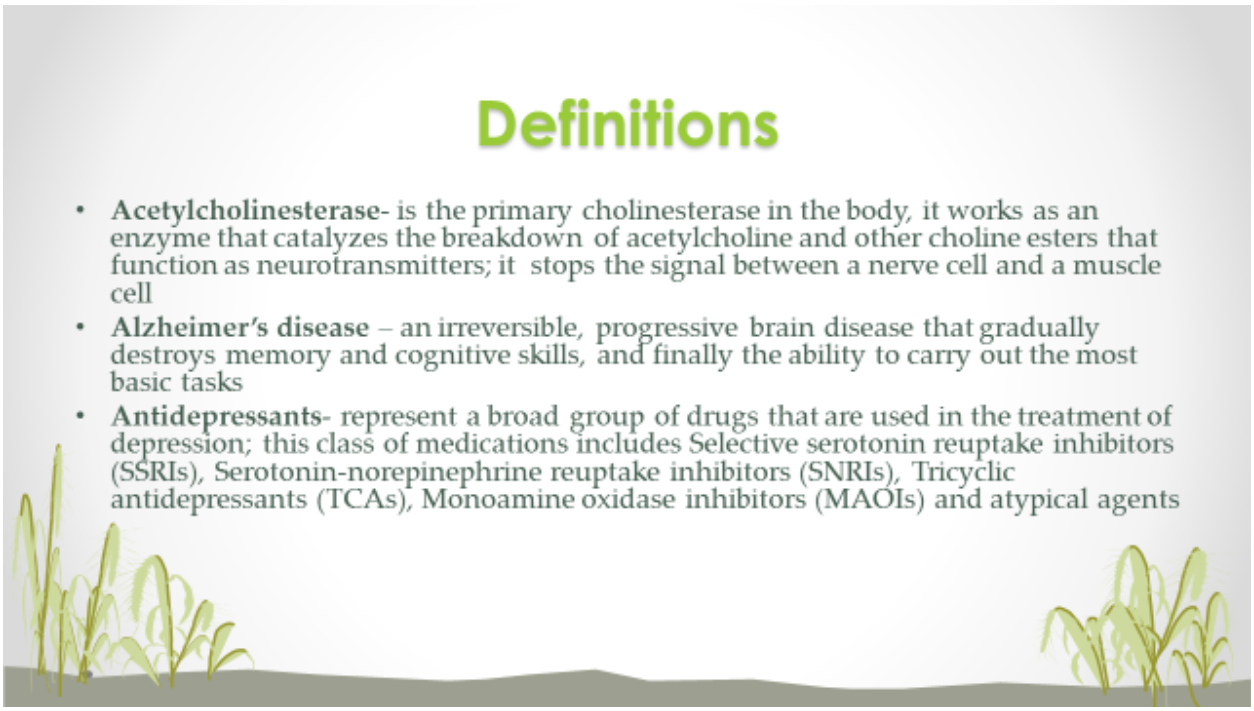

Introduction cont.
• Alzheimer's disease (AD) is a major public health problem and it affected 5.4 million individuals in 2014 in the United States. According to the Center for Disease Control and Prevention this number is projected to reach 13.8 million people in the US population by 2050 (CDC, 2016).
• The epidemiology of depression in AD has varied between different studies but it is estimated that it occurs in up to 50% in population of interest (Di Iulio et al., 2010).
• The Alzheimer's Association (Alzheimer's Association, 2017) estimates that Medicare and Medicaid will spend 68 percent of total costs on treatment of patients with AD and other dementias in 2017 and these costs will increase over 300 percent by 2050.

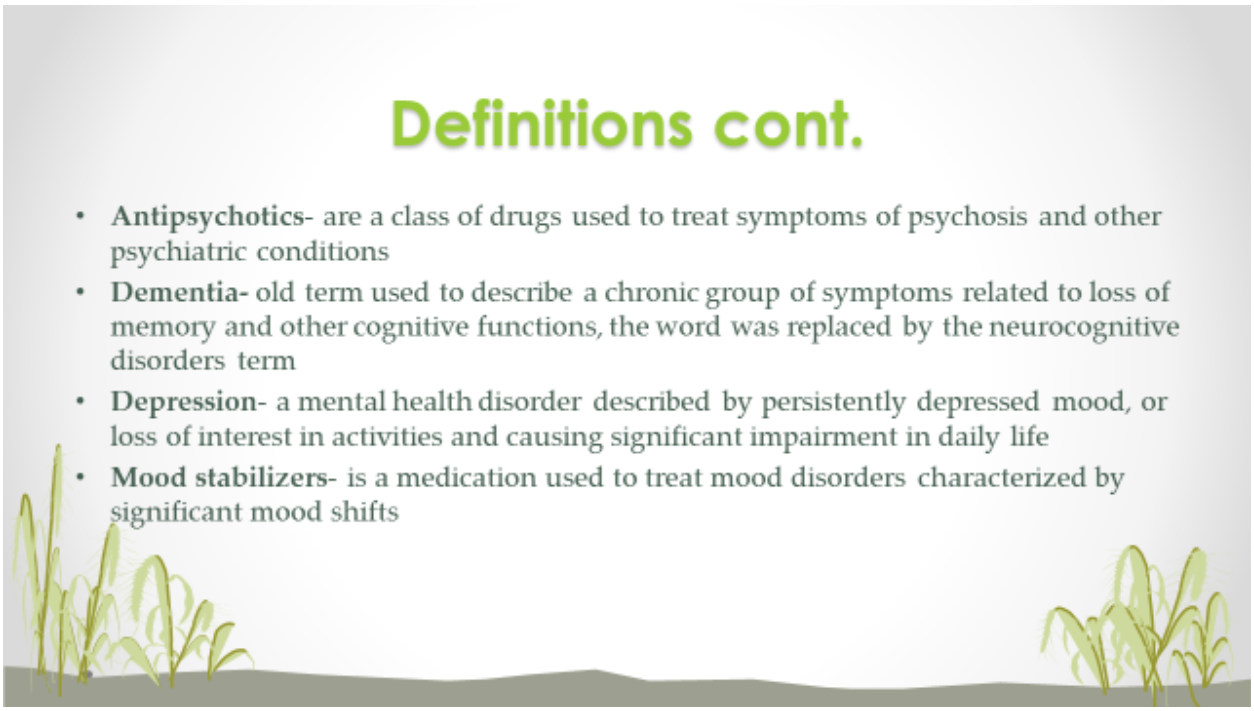

Purpose
Increase working knowledge and level of comfort of APPNs on depression in AD.
Increase level of care for the population of interest.
Identify key terms and definitions.
Describe methodology in psychiatric assessment.
Synthesize existing evidence-based best practice in non-pharmacological and pharmacological management of depression in AD.
Address interdisciplinary care.


Significance
Increasing number of individuals with Alzheimer's disease and comorbid depression increase APPNs probability of taking care of this population.
The Standards of Practice for Psychiatric Mental Health Nursing state that the psychiatric nurse "incorporates knowledge of pharmacological, biological and complementary interventions with applied clinical skills to restore the healthcare consumer's health and prevent further disability" (American Nurses Association, 2014, p.59).
APPNs need to integrate "ethical provisions in all areas of practice" (American Nurses Association, 2014, p.67) when it comes to applying nursing process in treatment of patients with depression in AD.

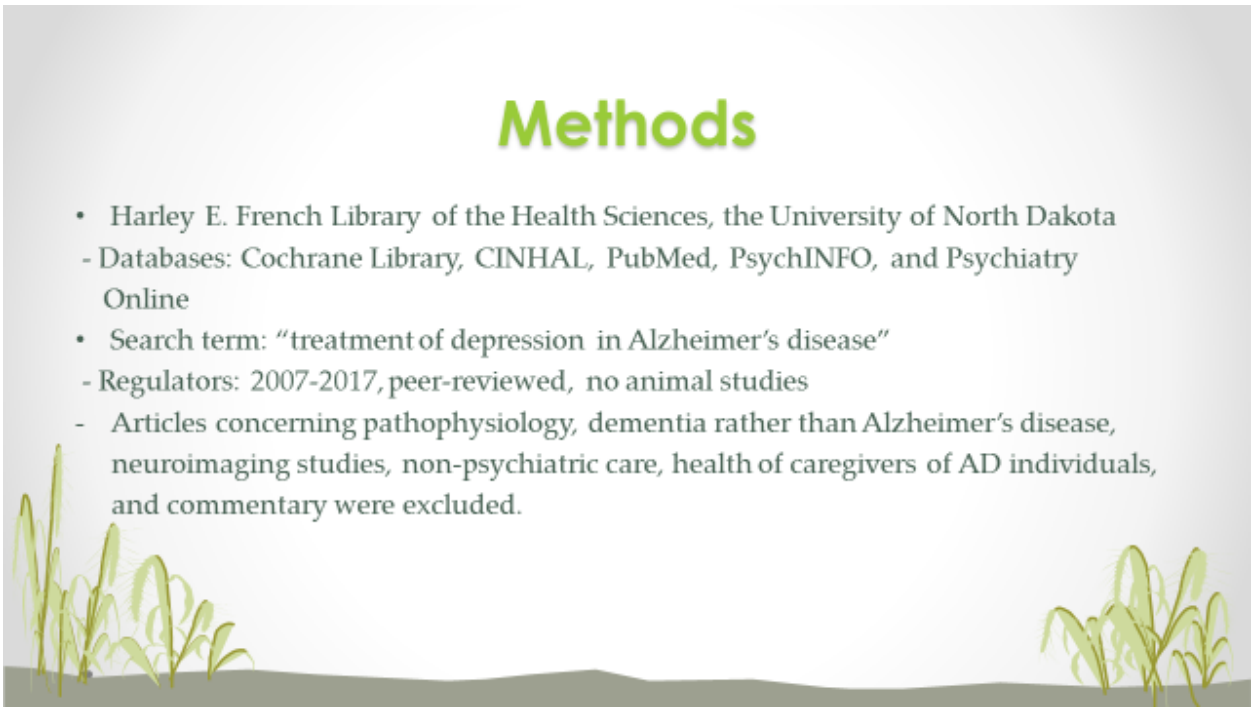

Theoretical Framework: Lenz and colleagues' Theory of Unpleasant Symptoms
• Purpose
- Lenz and Paugh (2008) explained the purpose of their theory stating that this theory can "improve understanding of the symptoms experience in various context and provide information useful for designing effective means to prevent, ameliorate, or manage unpleasant symptoms and their negative effects" (p.160).
• Major Concepts: three major components
- The symptoms that the individual is experiencing,
- Influencing factors that produce or affect the symptom experience,
- The consequences of the symptom experience.


Theoretical Framework: Lenz and colleagues' Theory of Unpleasant Symptoms cont.
• Terminology
- Symptoms are described in terms of duration, intensity, distress, and quality.
- Influencing factors can be physiologic factors, psychological factors and/or situational factors.
- Performance is illustrated in terms of functional status, cognitive functioning, or physical performance.
• Application
- It is clinically applicable to multiple patient situations because it should stimulate nurses to consider factors that might influence more than one symptom and the ways in which symptoms interact with each other (Lenz et al., 2008).

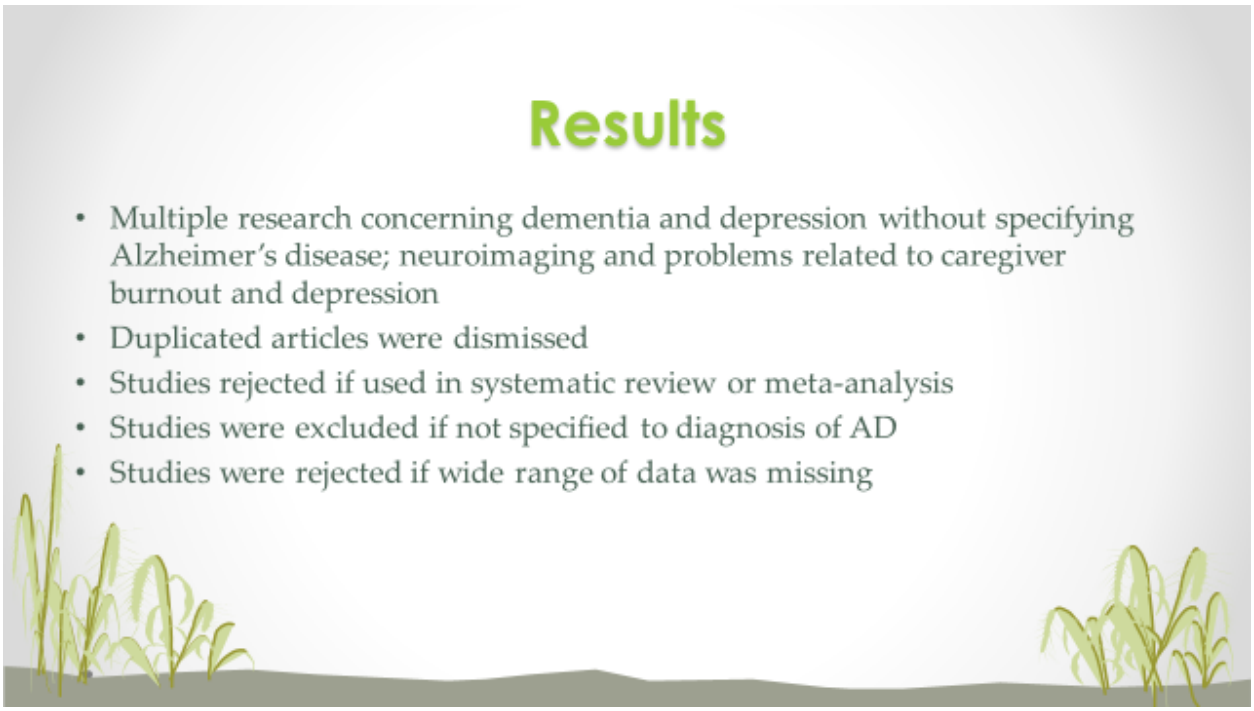

Definitions
Acetylcholinesterase- is the primary cholinesterase in the body, it works as an enzyme that catalyzes the breakdown of acetylcholine and other choline esters that function as neurotransmitters; it stops the signal between a nerve cell and a muscle cell
Alzheimer's disease – an irreversible, progressive brain disease that gradually destroys memory and cognitive skills, and finally the ability to carry out the most basic tasks
Antidepressants- represent a broad group of drugs that are used in the treatment of depression; this class of medications includes Selective serotonin reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs), Tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOIs) and atypical agents


Definitions cont.
Antipsychotics- are a class of drugs used to treat symptoms of psychosis and other psychiatric conditions
Dementia- old term used to describe a chronic group of symptoms related to loss of memory and other cognitive functions, the word was replaced by the neurocognitive disorders term
Depression- a mental health disorder described by persistently depressed mood, or loss of interest in activities and causing significant impairment in daily life
Mood stabilizers- is a medication used to treat mood disorders characterized by significant mood shifts

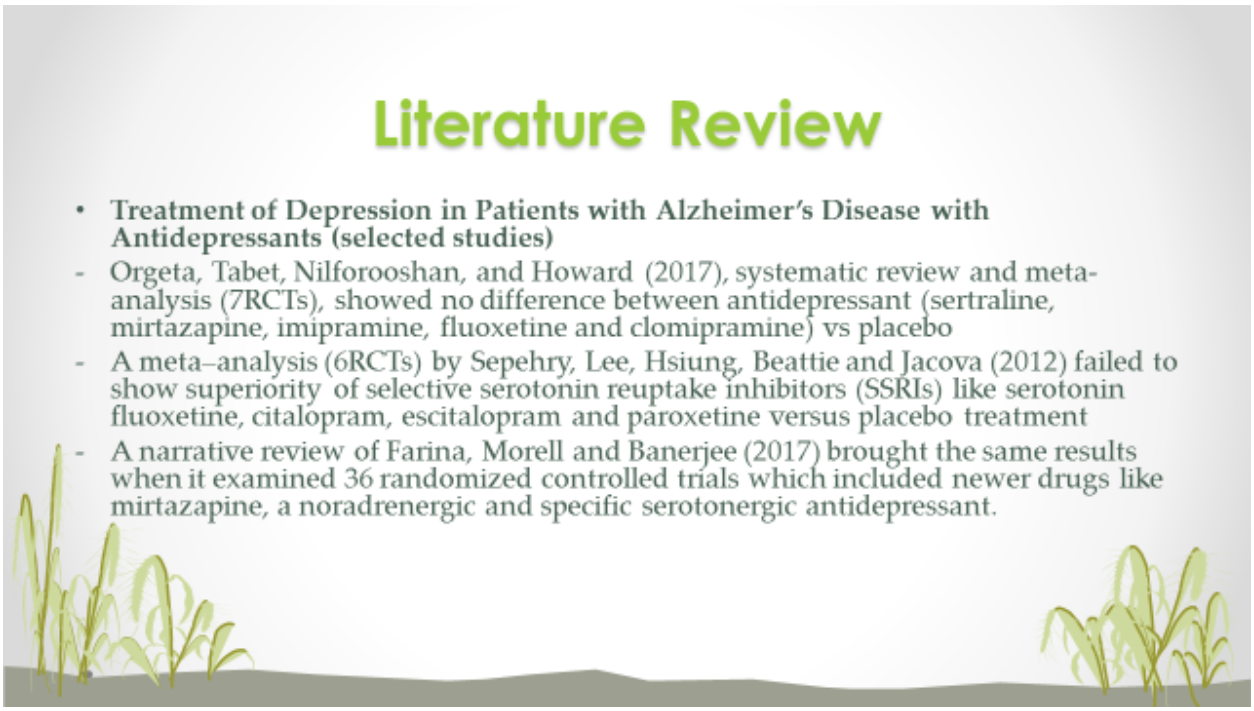

Definitions cont.
• Neurocognitive disorders- are characterized by decline in one or more cognitive areas like memory, attention, language, learning, perception and social skills
• Non-pharmacological treatment- is a treatment aimed at management of symptoms of a disease or condition which does not include pharmaceutical medications use, this treatment may include acupuncture, exercise, light therapy, music therapy and others
• Pharmacological treatment- management of condition by utilizing pharmaceutical medications

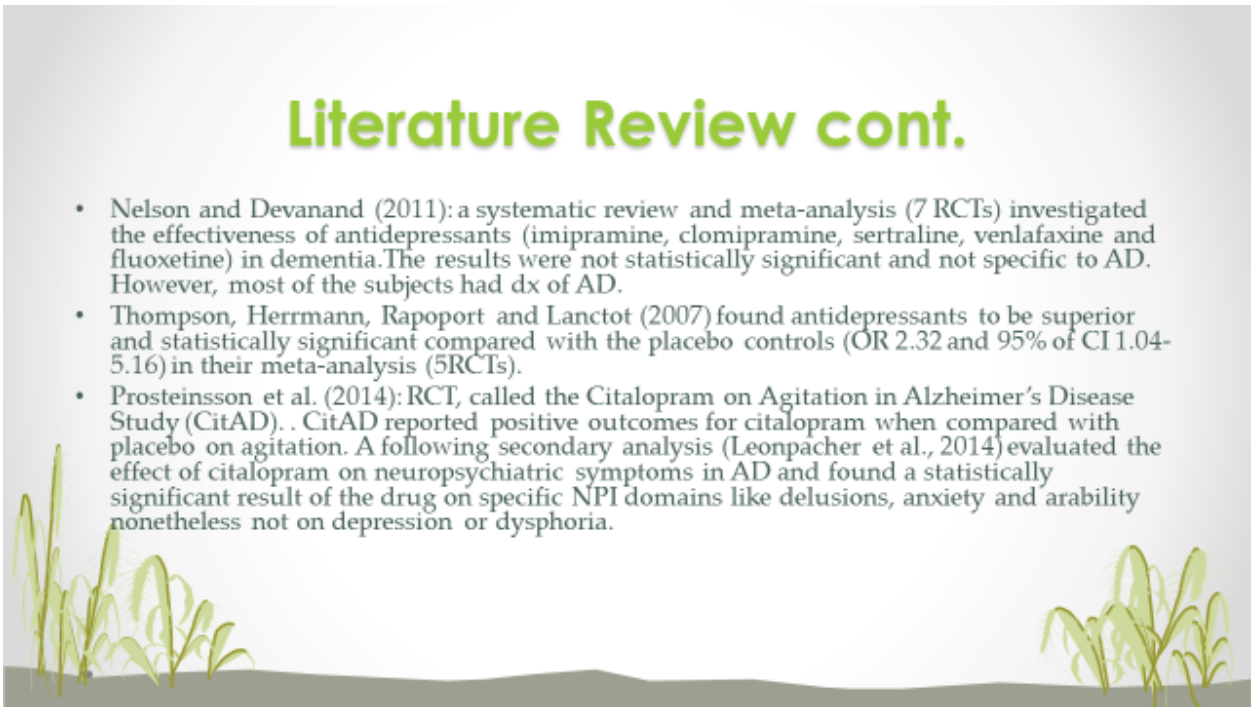

Methods
• Harley E. French Library of the Health Sciences, the University of North Dakota
- Databases: Cochrane Library, CINHAL, PubMed, PsychINFO, and Psychiatry Online
• Search term: "treatment of depression in Alzheimer's disease"
- Regulators: 2007-2017, peer-reviewed, no animal studies
- Articles concerning pathophysiology, dementia rather than Alzheimer's disease, neuroimaging studies, non-psychiatric care, health of caregivers of AD individuals, and commentary were excluded.

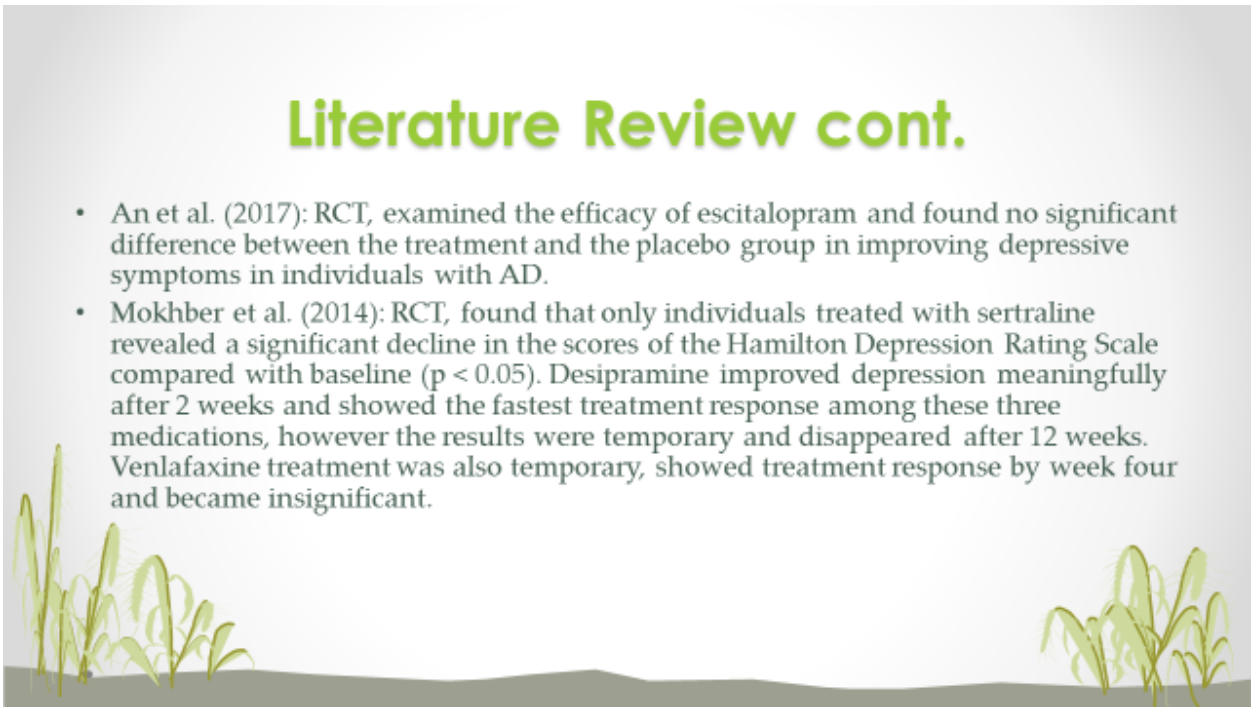

Methods cont.
• Manual search of references in reviewed articles performed
• Total articles appropriate for review: 93
• Standard of Care and Practice Parameters:
- American Association for Geriatric Psychiatry
- American Psychiatric Association
- Canadian Medical Association

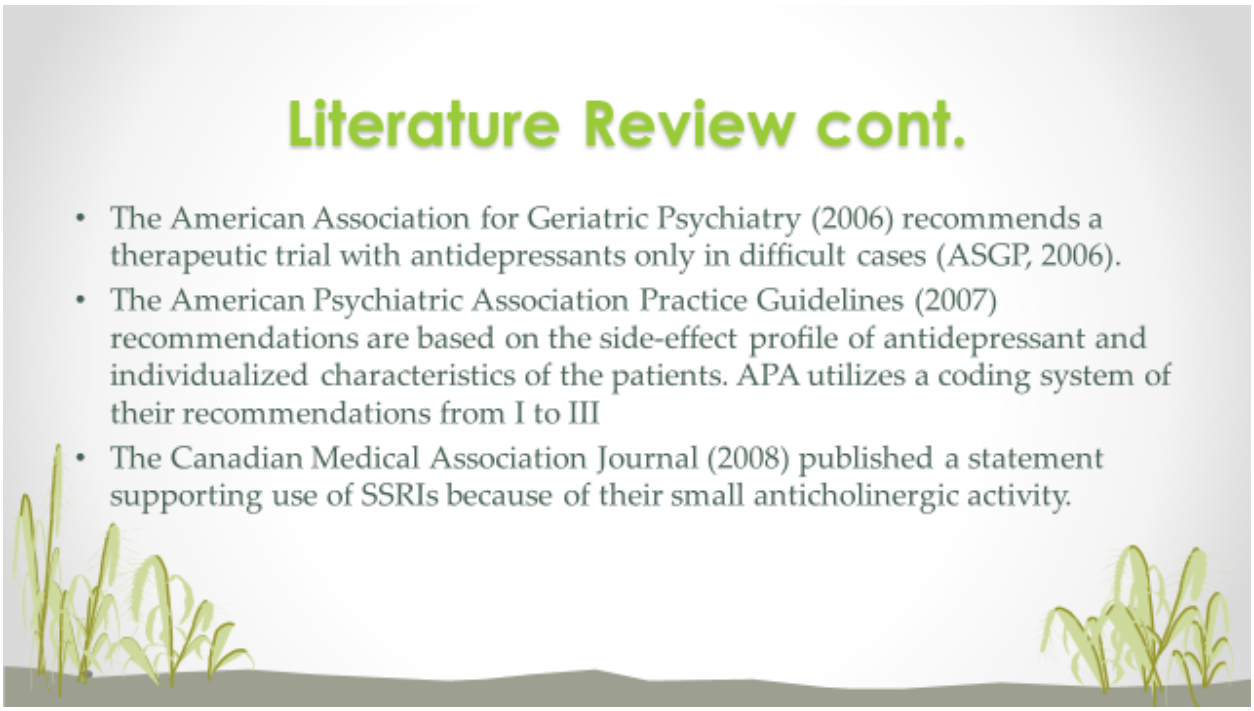

Results
Multiple research concerning dementia and depression without specifying Alzheimer's disease; neuroimaging and problems related to caregiver burnout and depression
Duplicated articles were dismissed
Studies rejected if used in systematic review or meta-analysis
Studies were excluded if not specified to diagnosis of AD
Studies were rejected if wide range of data was missing

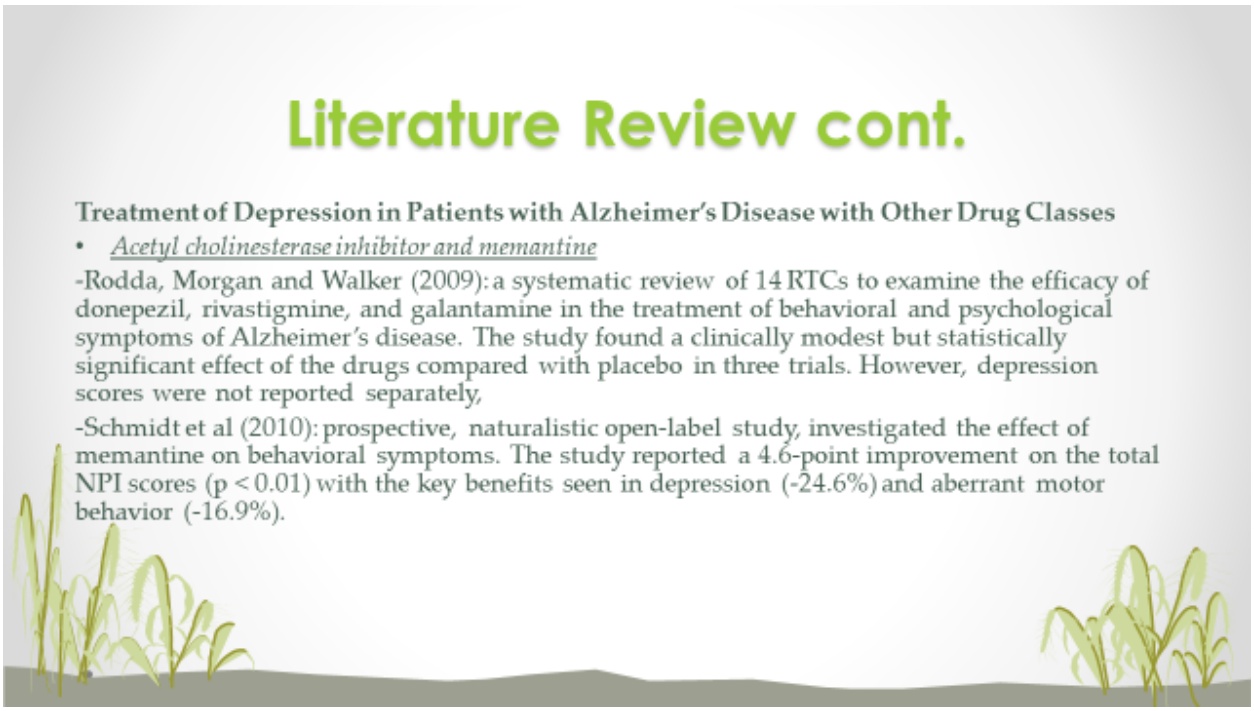

Search Results
Eleven randomized-controlled trials (RCTs)
Three systematic reviews
Three systematic reviews and meta-analysis
Two meta-analyses
Two open-label studies
Two secondary analyses
One narrative review
One quasi-experimental study

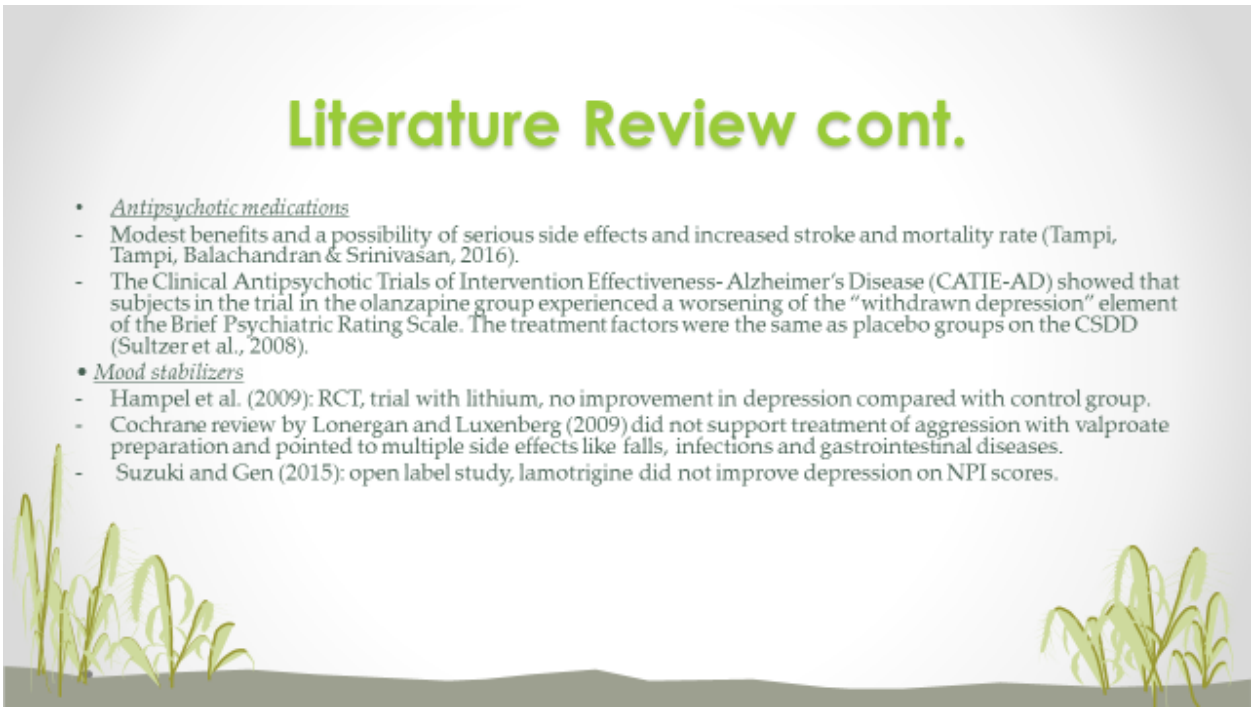

Literature Review
• Treatment of Depression in Patients with Alzheimer's Disease with Antidepressants (selected studies)
- Orgeta, Tabet, Nilforooshan, and Howard (2017), systematic review and meta-analysis (7RCTs), showed no difference between antidepressant (sertraline, mirtazapine, imipramine, fluoxetine and clomipramine) vs placebo
- A meta–analysis (6RCTs) by Sepehry, Lee, Hsiung, Beattie and Jacova (2012) failed to show superiority of selective serotonin reuptake inhibitors (SSRIs) like serotonin fluoxetine, citalopram, escitalopram and paroxetine versus placebo treatment
- A narrative review of Farina, Morell and Banerjee (2017) brought the same results when it examined 36 randomized controlled trials which included newer drugs like mirtazapine, a noradrenergic and specific serotonergic antidepressant.

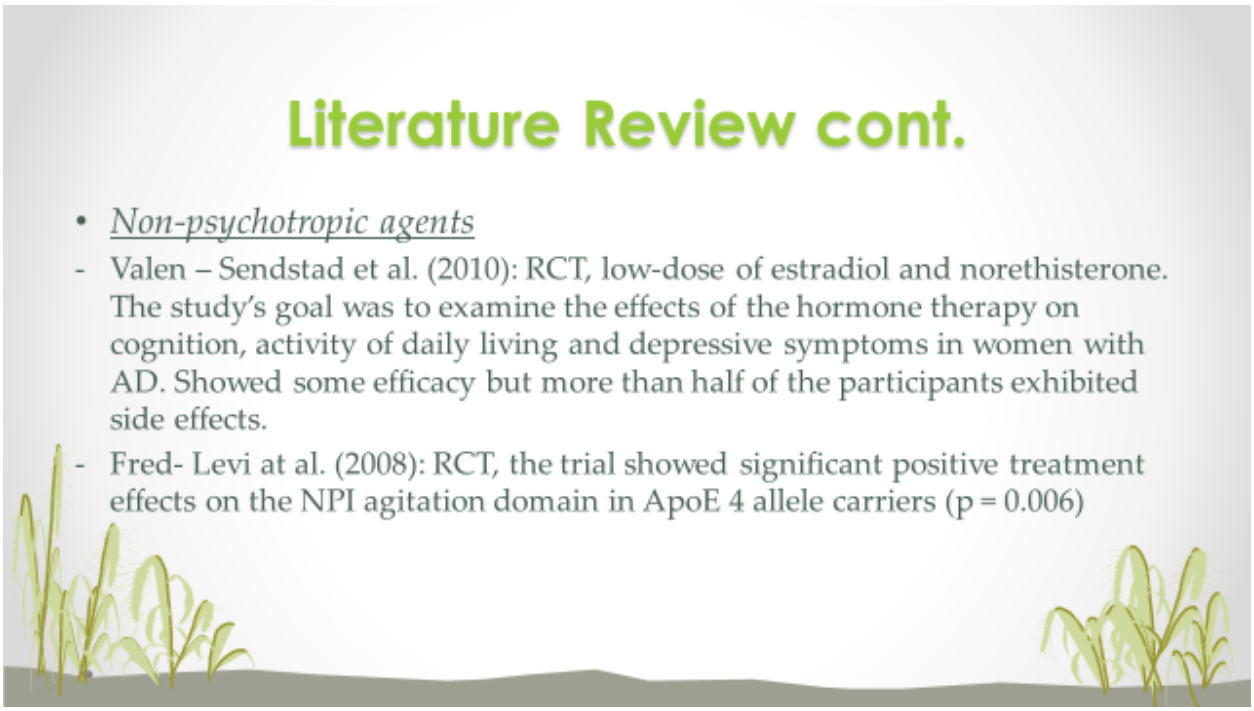

Literature Review cont.
• Nelson and Devanand (2011): a systematic review and meta-analysis (7 RCTs) investigated the effectiveness of antidepressants (imipramine, clomipramine, sertraline, venlafaxine and fluoxetine) in dementia.The results were not statistically significant and not specific to AD. However, most of the subjects had dx of AD.
• Thompson, Herrmann, Rapoport and Lanctot (2007) found antidepressants to be superior and statistically significant compared with the placebo controls (OR 2.32 and 95% of CI 1.04-5.16) in their meta-analysis (5RCTs).
• Prosteinsson et al. (2014): RCT, called the Citalopram on Agitation in Alzheimer's Disease Study (CitAD).. CitAD reported positive outcomes for citalopram when compared with placebo on agitation. A following secondary analysis (Leonpacher et al., 2014) evaluated the effect of citalopram on neuropsychiatric symptoms in AD and found a statistically significant result of the drug on specific NPI domains like delusions, anxiety and arability nonetheless not on depression or dysphoria.

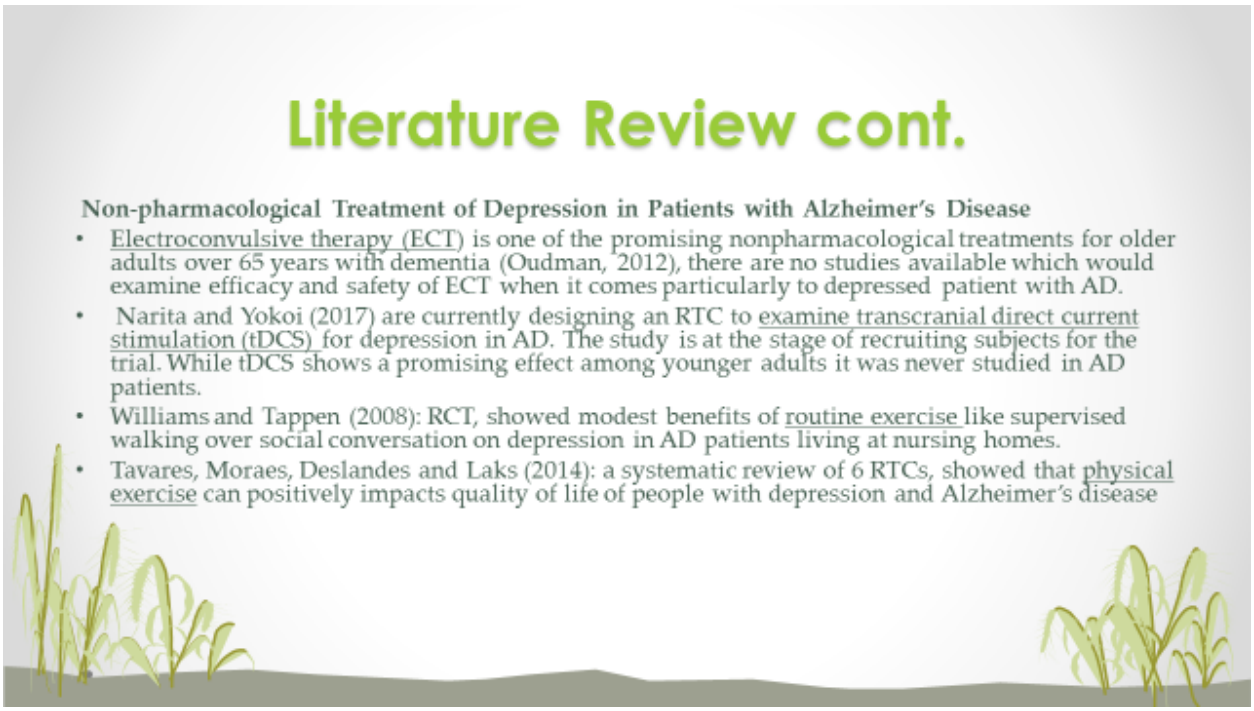

Literature Review cont.
An et al. (2017): RCT, examined the efficacy of escitalopram and found no significant difference between the treatment and the placebo group in improving depressive symptoms in individuals with AD.
Mokhber et al. (2014): RCT, found that only individuals treated with sertraline revealed a significant decline in the scores of the Hamilton Depression Rating Scale compared with baseline (p < 0.05). Desipramine improved depression meaningfully after 2 weeks and showed the fastest treatment response among these three medications, however the results were temporary and disappeared after 12 weeks. Venlafaxine treatment was also temporary, showed treatment response by week four and became insignificant.

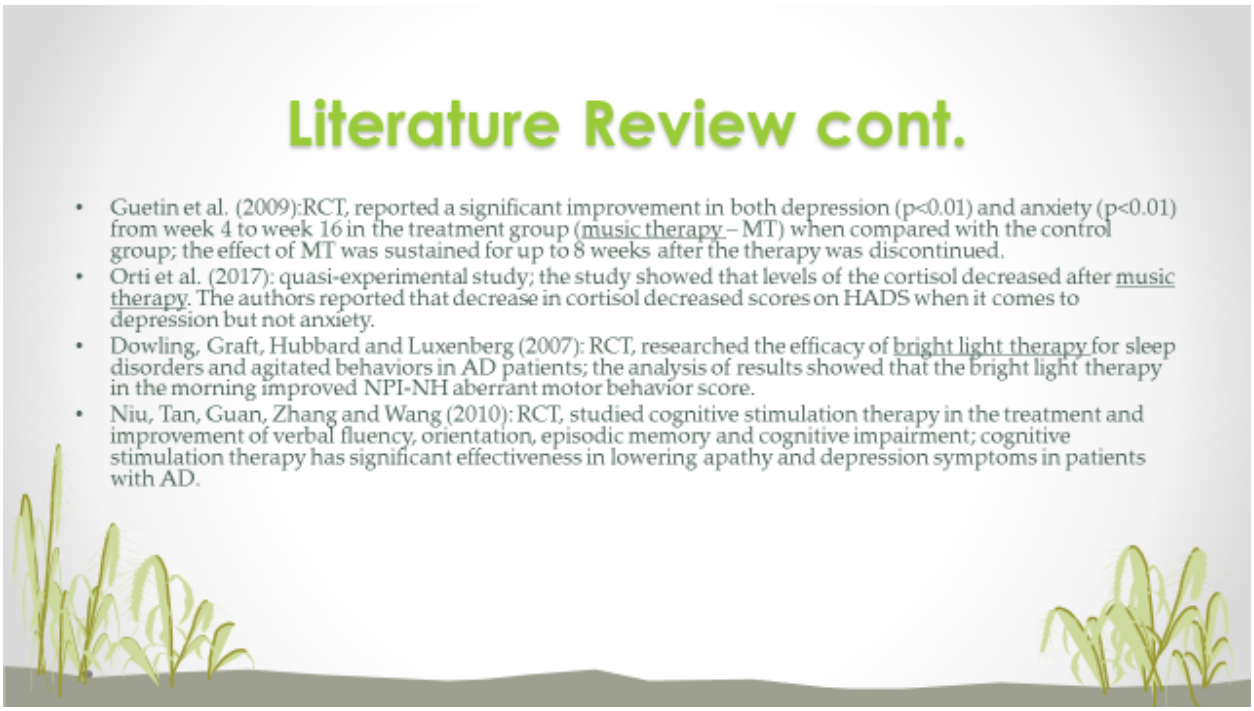

Literature Review cont.
• The American Association for Geriatric Psychiatry (2006) recommends a therapeutic trial with antidepressants only in difficult cases (ASGP, 2006).
• The American Psychiatric Association Practice Guidelines (2007) recommendations are based on the side-effect profile of antidepressant and individualized characteristics of the patients. APA utilizes a coding system of their recommendations from I to III
• The Canadian Medical Association Journal (2008) published a statement supporting use of SSRIs because of their small anticholinergic activity.

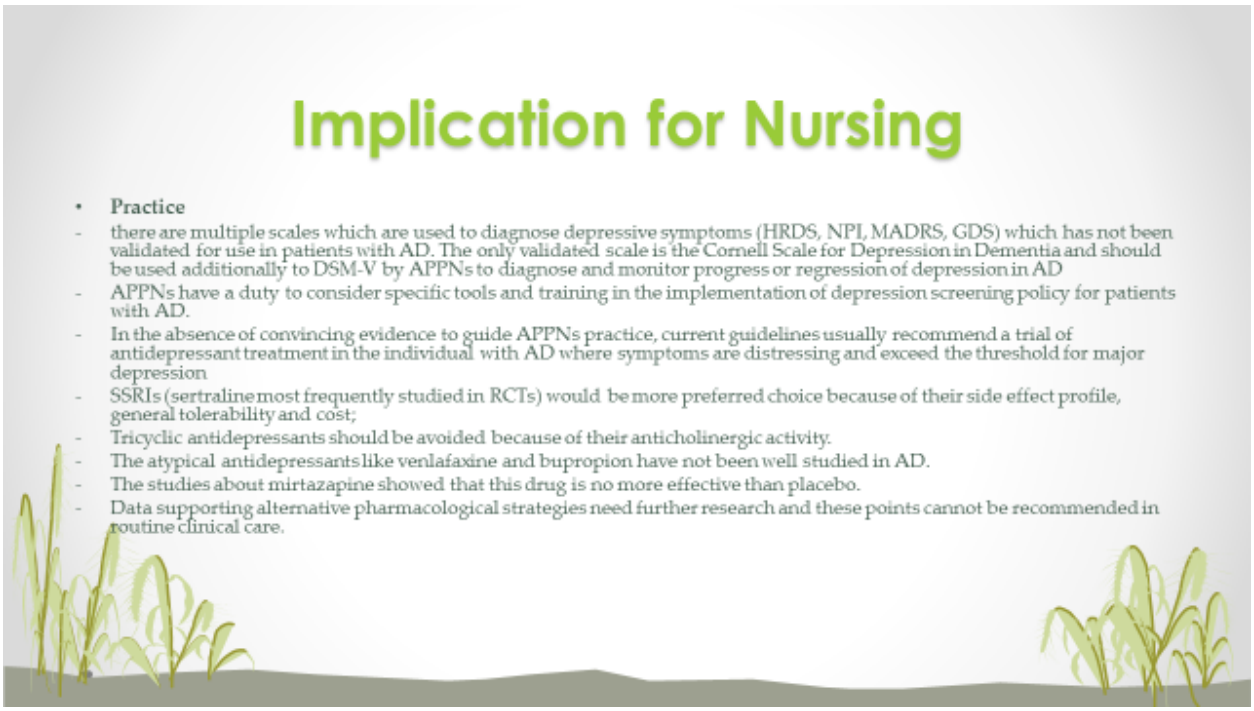

Literature Review cont.
Treatment of Depression in Patients with Alzheimer's Disease with Other Drug Classes
• Acetyl cholinesterase inhibitor and memantine
-Rodda, Morgan and Walker (2009): a systematic review of 14 RTCs to examine the efficacy of donepezil, rivastigmine, and galantamine in the treatment of behavioral and psychological symptoms of Alzheimer's disease. The study found a clinically modest but statistically significant effect of the drugs compared with placebo in three trials. However, depression scores were not reported separately,
-Schmidt et al (2010): prospective, naturalistic open-label study, investigated the effect of memantine on behavioral symptoms. The study reported a 4.6-point improvement on the total NPI scores (p < 0.01) with the key benefits seen in depression (-24.6%) and aberrant motor behavior (-16.9%).

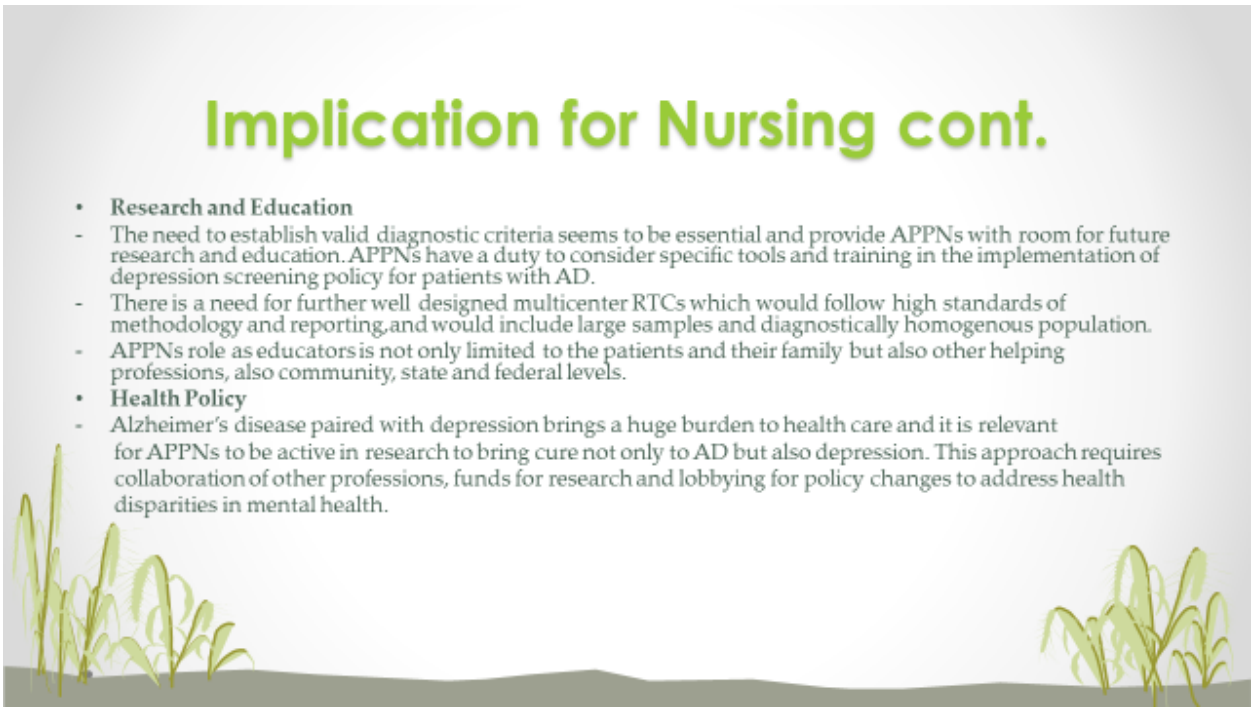

Literature Review cont.
• Antipsychotic medications
- Modest benefits and a possibility of serious side effects and increased stroke and mortality rate (Tampi, Tampi, Balachandran & Srinivasan, 2016).
- The Clinical Antipsychotic Trials of Intervention Effectiveness- Alzheimer's Disease (CATIE-AD) showed that subjects in the trial in the olanzapine group experienced a worsening of the "withdrawn depression" element of the Brief Psychiatric Rating Scale. The treatment factors were the same as placebo groups on the CSDD (Sultzer et al., 2008).
• Mood stabilizers
- Hampel et al. (2009): RCT, trial with lithium, no improvement in depression compared with control group.
- Cochrane review by Lonergan and Luxenberg (2009) did not support treatment of aggression with valproate preparation and pointed to multiple side effects like falls, infections and gastrointestinal diseases.
- Suzuki and Gen (2015): open label study, lamotrigine did not improve depression on NPI scores.


Literature Review cont.
• Non-psychotropic agents
- Valen – Sendstad et al. (2010): RCT, low-dose of estradiol and norethisterone. The study's goal was to examine the effects of the hormone therapy on cognition, activity of daily living and depressive symptoms in women with AD. Showed some efficacy but more than half of the participants exhibited side effects.
- Fred- Levi at al. (2008): RCT, the trial showed significant positive treatment effects on the NPI agitation domain in ApoE 4 allele carriers (p = 0.006)


Literature Review cont.
Non-pharmacological Treatment of Depression in Patients with Alzheimer's Disease
• Electroconvulsive therapy (ECT) is one of the promising nonpharmacological treatments for older adults over 65 years with dementia (Oudman, 2012), there are no studies available which would examine efficacy and safety of ECT when it comes particularly to depressed patient with AD.
• Narita and Yokoi (2017) are currently designing an RTC to examine transcranial direct current stimulation (tDCS) for depression in AD. The study is at the stage of recruiting subjects for the trial. While tDCS shows a promising effect among younger adults it was never studied in AD patients.
• Williams and Tappen (2008): RCT, showed modest benefits of routine exercise like supervised walking over social conversation on depression in AD patients living at nursing homes.
• Tavares, Moraes, Deslandes and Laks (2014): a systematic review of 6 RTCs, showed that physical exercise can positively impacts quality of life of people with depression and Alzheimer's disease


Literature Review cont.
• Guetin et al. (2009):RCT, reported a significant improvement in both depression (p<0.01) and anxiety (p<0.01) from week 4 to week 16 in the treatment group (music therapy – MT) when compared with the control group; the effect of MT was sustained for up to 8 weeks after the therapy was discontinued.
• Orti et al. (2017): quasi-experimental study; the study showed that levels of the cortisol decreased after music therapy. The authors reported that decrease in cortisol decreased scores on HADS when it comes to depression but not anxiety.
• Dowling, Graft, Hubbard and Luxenberg (2007): RCT, researched the efficacy of bright light therapy for sleep disorders and agitated behaviors in AD patients; the analysis of results showed that the bright light therapy in the morning improved NPI-NH aberrant motor behavior score.
• Niu, Tan, Guan, Zhang and Wang (2010): RCT, studied cognitive stimulation therapy in the treatment and improvement of verbal fluency, orientation, episodic memory and cognitive impairment; cognitive stimulation therapy has significant effectiveness in lowering apathy and depression symptoms in patients with AD.


Implication for Nursing
• Practice
- there are multiple scales which are used to diagnose depressive symptoms (HRDS, NPI, MADRS, GDS) which has not been validated for use in patients with AD. The only validated scale is the Cornell Scale for Depression in Dementia and should be used additionally to DSM-V by APPNs to diagnose and monitor progress or regression of depression in AD
- APPNs have a duty to consider specific tools and training in the implementation of depression screening policy for patients with AD.
- In the absence of convincing evidence to guide APPNs practice, current guidelines usually recommend a trial of antidepressant treatment in the individual with AD where symptoms are distressing and exceed the threshold for major depression
- SSRIs (sertraline most frequently studied in RCTs) would be more preferred choice because of their side effect profile, general tolerability and cost;
- Tricyclic antidepressants should be avoided because of their anticholinergic activity.
- The atypical antidepressants like venlafaxine and bupropion have not been well studied in AD.
- The studies about mirtazapine showed that this drug is no more effective than placebo.
- Data supporting alternative pharmacological strategies need further research and these points cannot be recommended in routine clinical care.


Implication for Nursing cont.
• Research and Education
- The need to establish valid diagnostic criteria seems to be essential and provide APPNs with room for future research and education. APPNs have a duty to consider specific tools and training in the implementation of depression screening policy for patients with AD.
- There is a need for further well designed multicenter RTCs which would follow high standards of methodology and reporting,and would include large samples and diagnostically homogenous population.
- APPNs role as educators is not only limited to the patients and their family but also other helping professions, also community, state and federal levels.
• Health Policy
- Alzheimer's disease paired with depression brings a huge burden to health care and it is relevant for APPNs to be active in research to bring cure not only to AD but also depression. This approach requires collaboration of other professions, funds for research and lobbying for policy changes to address health disparities in mental health.


Questions?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