Depressive Episodes in Patients with Newly-Diagnosed Early-Onset Dementia versus Late-Onset Dementia

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DEPRESSIVE EPISODES IN PATIENTS WITH NEWLY-DIAGNOSED EARLY-ONSET DEMENTIA VS LATE-ONSET DEMENTIA

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

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List of Abbreviations

AD – Alzheimer’s Disease/Dementia
CSDD – Cornell Scale for Depression in Dementia
DLB – Dementia with Lewy Bodies
EOAD – Early-onset Alzheimer’s Disease
EOD – Early-onset Dementia
FTD – Frontotemporal Dementia
GDS – Global Deterioration Scale
HIV – Human Immunodeficiency Virus
LAR – Legally Authorized Representative
LOAD – Late-onset Alzheimer’s Disease
LOD – Late-onset Dementia
MDD – Major Depressive Disorder
MMSE – Mini Mental State Examination
NPI – Neuropsychiatric Inventory
SSRIs – Selective Serotonin Reuptake Inhibitors
TBI – Traumatic Brain Injury
VaD – Vascular Dementia

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Abstract

Dementia is an irreversible decline in cognition, which is most commonly seen in the elderly, but a minority of patients are diagnosed before the age of 65, in a subtype known as early-onset dementia. There is a strong association between dementia and major depression in the elderly, but the prevalence of depression in patients with early-onset dementia lacks consensus among existing studies, and there is a paucity of data in newly diagnosed individuals. We propose a cross-sectional study to measure the prevalence ratio of major depression in patients with early-onset dementia compared to those over the age of 65. Specifically, we aim to administer the Cornell Scale for Depression in Dementia to dichotomize the presence of a major depressive episode in newly diagnosed individuals with early-onset dementia when compared to those over 65 years-old. This study may improve our understanding of disease burden in patients with dementia of various ages.
Chapter 1: Introduction

1.1 Background

According to DSM-V criteria, dementia is diagnosed based on evidence of significant cognitive decline that interferes with independence in everyday activities.\(^1\) The cognitive decline cannot be reversible. Dementia increases in prevalence with age, approximately doubling in prevalence every 5 years after the age of 65.\(^2\) Early-onset dementia (EOD), sometimes referred to as “young-onset dementia” or “presenile dementia”, is a subcategory of dementia that affects patients less than 65 years old, while late-onset dementia (LOD) represents patients with dementia over 65 years old. According to a systematic review, EOD is far less common than LOD and comprises approximately 5.5% of patients with dementia.\(^3\) Although some studies suggest that EOD may comprise a much higher percentage of overall dementia – up to 29.3% in the US.\(^4\)

The four most common types of dementia are Alzheimer’s disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD), with AD being the most common of the four. A systematic review of studies estimating the prevalence of different types of dementia reviewed 73 studies published from 1985 to 2012 and found that estimated prevalence varied by large percentages between studies.\(^4\) The estimated prevalence of AD in EOD, also referred to as early-onset Alzheimer’s dementia (EOAD), represents the largest proportion of EOD and was found to be the most common etiology in the studies examined. EOAD estimates ranged between 1% to 66.7%. VaD in EOD comprises 4.3% to 42.5% of EOD. FTD in EOD comprises 3% to 26.6% of EOD. Finally, DLB is frequently reported as the lowest prevalence of EOD at less than 1% to 7% of EOD.\(^4\) While studies examined generally
found AD to be the most prevalent, VaD to be 2nd most common, FTD to be 3rd most common, and DLB to be the least common, the differences between studies are attributed to selection bias, different populations, and varying methods of study.

Depression affects a large number of elderly individuals and has been associated heavily with dementia.\textsuperscript{5} Systematic reviews have estimated that 25% to 50% of patients with dementia have depression.\textsuperscript{6,7} However, due to dementia incidence rising with age, most of the studies examining the prevalence of depression in dementia examined patients greater than 65 years old. In AD specifically, it has been estimated that 20-30% of patients with AD have depression and that other forms of dementia including VaD and DLB tend to have higher rates of depression than AD.\textsuperscript{8} A meta-analysis of modifiable risk factors of AD found that depression significantly increases the risk of developing AD.\textsuperscript{9} Additionally, many risk factors for AD are shared with risk factors for depression including that individuals are less likely to engage in physical and cognitive activities.\textsuperscript{10} Post-mortem studies suggest that patients with AD and a history of major depression have an increased number of beta-amyloid plaques and neurofibrillary tangles (neuropathological markers of AD) when compared to those with AD without a history of depression.\textsuperscript{11} There are several screening tools utilized to screen for and help diagnose depression in patients with dementia – the most popular being the Cornell Scale for Depression in Dementia (CSDD) and the Geriatric Depression Scale.\textsuperscript{12-14}

Dementia and depression are both associated with higher rates of mortality, morbidity, and have a high burden on caregivers.\textsuperscript{15,16} Patients with EOD have been shown to have a higher burden of disease, worse cognitive impairment scores, and worse executive function when compared to those with LOD with comparable disease
The burden of care for dementia frequently falls on family members and has a significant social, financial, physical, and emotional impact on caregivers.\textsuperscript{17,18} In patients with both depression and dementia, the burden on caregivers has been shown to be higher than dementia alone.\textsuperscript{19} In 2015, the average economic cost of dementia per patient per year in the United States has been estimated to be $50,000 across all severities.\textsuperscript{20} The higher the severity of the disease, the higher the cost of care.

Depression in the presence of dementia is typically treated with selective serotonin reuptake inhibitors (SSRIs), but evidence of efficacy is mixed.\textsuperscript{21,22} Other forms of non-drug interventions have also been utilized with varying efficacy including exercise and cognitive stimulation.\textsuperscript{23}

While many studies have shown a strong association between depression and dementia, few have analyzed the association between depressive symptoms and EOD vs LOD. Considering EOD affects approximately 81 to 113 per 100,000 people of the general population (aged 45-65)\textsuperscript{24}, a study that better elucidates the relationship of depression in EOD is needed. Knowing the prevalence ratio of depression in patients with EOD vs LOD will improve understanding of disease burden and may lead to increased screening of depression in patients with newly-diagnosed dementia of all ages.

1.2 Statement of the Problem

The prevalence ratio of depression among those with early-onset dementia compared to late-onset dementia is not well established, nor consistent among existing studies. One multicenter study from Norway, Denmark, and Iceland found a different median score of depression as measured by CSDD: 6.0 (IQR of 7) for EOD, and 7.0 (IQR
of 7) for LOD, although it was not statically significant \((p = 0.123)\), and the study’s primary outcome sought quality of life measures rather than depression.\(^{25}\) A study out of The Netherlands found that the prevalence of depression was lower in patients with EOAD when compared to late-onset Alzheimer’s disease (LOAD) \((\text{OR} = 0.23, 95\% \text{ CI} = 0.10–0.53, p = 0.001)\).\(^{26}\) A study of rural populations in Canada found no significant difference in depression between EOD and LOD.\(^{27}\) Although none of the studies mentioned sought the same primary outcome, nor did they have similar populations. Additionally, data pertaining to depression prevalence around the time of diagnosis in populations of EOD and LOD seem to be lacking.

### 1.3 Goals & Objectives

Establish a prevalence ratio of patients with a probable presence of a major depressive episode by the Cornell Scale of Depression in Dementia (CSDD) score of 10 or greater, of those with newly diagnosed early-onset dementia to those with newly diagnosed late-onset dementia. Reported anxiety levels and depressive symptom severity will also be measured by the CSDD and compared as a secondary objective.

### 1.4 Hypothesis

We hypothesize that adults aged less than 65 with a newly diagnosed early-onset dementia will have a statistically different prevalence ratio of major depression when compared to adults aged 65 or older with newly diagnosed late-onset dementia.
References


Chapter 2: Review of the Literature

2.1 Introduction

Over the period of August 2021 to July 2022, periodic searches were performed using the Cochrane library, PubMed, Ovid Medicine, and Scopus with key search terms. Due to the lack of Mesh search terms for early-onset dementia, the following terms were included as primary search terms: Early-Onset Dementia, Young-Onset Dementia, Early-Onset Alzheimer*, Young-Onset Alzheimer*, Early-Onset AD, Young-Onset AD, EOAD (early-onset Alzheimer’s disease), YOAD (young-onset Alzheimer’s disease), EOD (early-onset dementia), YOD (young-onset Alzheimer’s disease). Mesh search terms for depression and depressive disorder, major were included in the search. Additional key terms included were depressive, depression. Articles written in the past 10 years were given precedence. Pertinent clinical or observational studies, systematic reviews, meta-analyses, and randomized control trials (RCTs) were utilized. All articles examined were limited to those written in the English language, regardless of the location of study. To identify further relevant material, additional articles were found in the reference lists of the articles discovered in our primary search. Preliminary screening of articles was performed by analyzing the abstracts and titles and eliminating non-relevant articles.

By reviewing existing and pertinent studies, along with their limitations, we intend to demonstrate how this proposed cross-sectional study will be novel and fill in existing gaps in the literature.
2.2 Review of Empirical Studies

There are few studies that have examined the relationship between depression and EOD as a primary outcome. Some studies have measured secondary outcomes of depression in patients with EOD vs LOD with mixed results.1-3 Additionally, several of the studies reviewed examined patients exclusively with Alzheimer’s dementia, and did not include patients with other forms of dementia such as VaD, FTD, or LBD. Since AD represents the largest share of EOD and LOD, we felt it pertinent to include them in our review.

A 2018 multicenter Nordic cross-sectional study was performed to assess quality of life (QOL) in patients with early-onset dementia in those with Alzheimer’s disease and frontotemporal dementia.1 These patients were enrolled from 10 clinics in Iceland, Norway, and Denmark. This multicenter study looked recruited 88 EOD patients with 50 patients with AD and 38 with FTD. They compared their participants to 100 patients with LOD. For their primary outcome of QOL, they utilized a proxy of a self-reported questionnaire called the Euro-QoI-5 Dimensions 3 level version. To examine the secondary outcome of depressive symptoms, they utilized two measures including the CSDD and the Montgomery Åsberg Depression Rating Scale. When the total number of patients with EOD were compared to LOD using the CSDD, there was a non-significant change in CSDD score: Total EOD 5.0 (IQR of 7) vs LOD 7.0 (IQR of 7) with p = 0.123, thus they were unable to show a meaningful difference in prevalence ratio of depression between the two groups. However, in a post hoc analysis of the association between CSDD score and QOL, for those participants with a higher CSDD score, they showed a negative association with poorer QOL (mean per standard deviation: -0.610, CI: -0.868 to
-0.352, p < 0.001). One limitation of this study to be noted is that the QOL measurements were only obtained on those who were classified as having mild cognitive impairment and does not necessarily represent those with more severe forms of cognitive impairment. Additionally, due to the requirement of informed consent, there may have been increased selection bias that may have excluded those with more severe dementia or those with a higher burden of illness at baseline.¹

A 2012 Dutch prospective cohort study (NeedYD study) examined incidence, prevalence, and persistence of neuropsychiatric symptoms, including depression, in 98 patients with EOAD.³ For comparison they utilized 132 patients with LOAD from a separate 2-year prospective cohort study (Maastricht Study of Behavior in Dementia) which was structured with a similar design and diagnostic criteria.⁴ The study utilized the Dutch version of the Neuropsychiatric Inventory (NPI) for assessment of any depressive symptoms but did not assess for major depression. Over a two-year period, the study found the cumulative prevalence for those with EOAD had fewer depressive symptoms (40.5%) (OR = 0.23, 95% CI = 0.10–0.53, p = 0.001) compared with the LOAD group (72.1%). A possible limitation includes the use of a LOAD group from an older study and potential historical differences in medications prescribed to patients. The study did not control for medication use of subjects at baseline, nor accounted for changes in medications during the 2 years of follow-up.

A 2020 cross-sectional study out of a remote and rural memory clinic in Western Canada examined 61 patients with EOD and 272 patients with LOD. The study assessed neuropsychiatric symptoms as well as differences in mood, behavior, social factors, and function.² Over a period of 12 years from 2004 to 2016, all eligible patients and
Caregivers were given questionnaires to assess symptoms and social factors. The study utilized age at diagnosis to determine whether patients should be grouped into EOD or LOD groups. For measurements of depression, the study utilized the depressed mood scale (CES-D scale) which has a maximum score of 60, with higher scores having higher symptomatology. The study found that patients with EOD had statistically significant higher rates of depression than those with LOD (16.7 ± 9.3 compared to 12.3 ± 8.9, p = 0.002). Given that the study was conducted serving rural patients, the results may differ from urban populations limiting the generalizability of the study. Additionally, this study did not control for any confounding variables.

A small 2017 cross-sectional study out of Portugal compared neuropsychiatric symptoms, including depression, of 35 patients with EOAD and 35 patients with late-onset Alzheimer’s dementia. The patients were selected retrospectively from those previously diagnosed with EOAD and then matched to similar patients with LOAD, controlling for demographic variables and disease severity. Patients were recruited from a single memory center. Utilizing the Portuguese version of the NPI, the study found no statistically significant difference between depression/dysphoria of EOAD and LOAD (prevalence of 40.0% vs 51.4%, p = 0.268). Given the small sample size, the study may have lacked statistical power.

The four studies above all directly examined the relationship between depressive symptoms in EOD vs LOD but found different results: The Nordic study and Portuguese study found no statistical significance, the Dutch study found increased depressive symptoms in those with LOD, and the rural Canada study found higher rates of depression in those with EOD. Additionally, populations between the studies varied
significantly and would not necessarily reflect similar results with a US population in an urban area.

While the studies mentioned examined depressive symptoms between the EOD and LOD groups as part of a neuropsychiatric profile or as a measure of QOL, they did not examine patients with dementia with previously diagnosed depression. A 2014 cross-sectional analysis examined and compared 614 patients with EOAD and 3,133 patients with LOAD from an existing database for differences in demographics, comorbidities (including diagnosis of anxiety or depression), and prescribed medications. The study found that patients with EOAD were more likely to have a previous comorbid diagnosis of anxiety or depression (OR 1.7, 95% CI 1.34–2.27, p < 0.0001) than patients with LOAD. However, the study did not account for dementia severity, and due to the study design did not assess if patients had active depressive symptoms or depressive episodes, thus possibly missing patients with depression without a preexisting diagnosis.

The aim of this study will be to assess probable major depressive episodes in patients with EOD vs patients with LOD, therefore it is important to understand how prevalent the condition of major depression is in these populations. An older 2005 statistical analysis examined 670 patients with AD. The study did not compare patients with EOAD vs LOAD and a majority of the patients would be classified in the LOAD category based on demographic age measurements (mean age 72.8, SD 7.2). The study showed that 26% (n = 177) of AD patients had major depression, 26% (n = 177) had minor depression and 48% (n = 316) were not depressed. While this study did not examine EOD patients, it gives a possible estimate of the number of patients to be expected with major depression and dementia.
2.3 Confounding Variables

Depression and dementia share many of the same risk factors and have been shown to influence each other, which makes isolating potential confounding variables difficult. Depression has been associated as a possible prodrome and risk factor of dementia.\(^9\)

A 2013 systematic review of case-control and cohort studies looking at the patients with affective disorders and the risk of developing dementia, found 3 studies that showed that bipolar disorder had a statistically significant higher risk of developing dementia compared to patients with unipolar depression alone. Depression is a significant feature of bipolar disorder. The studies examined did not frequently account for patients with bipolar disorder, but sometimes excluded patients with previous psychiatric history, which would likely include bipolar disorder.

Down Syndrome, also known as Trisomy 21, has been shown to have higher rates of both depression and AD when compared to the general population.\(^{10,11}\) In fact, the most common cause of dementia occurring in patients in their 30s is Down Syndrome.\(^{12}\) The Dutch and Nordic studies mentioned above, excluded patients with dementia caused by Down Syndrome to account for confounding.\(^{1,3}\)

In addition to Down Syndrome, other etiologies of dementia such as dementia caused by traumatic brain injuries (TBI), human immunodeficiency virus (HIV), Huntington’s disease, or alcohol-related are often excluded from studies examining EOD as these conditions are treated as distinct cognitive disorders that from dementia.
Depressive symptoms may be attributable to all of these conditions as well, which could create potential confounding if included.

Race is a possible variable to account for between EOD and LOD groups. A 2014 global cross-sectional analysis of existing data on patients with EOAD and LOAD found that there was an increased odds ratio for developing EOAD vs LOAD among other races (including Alaskan natives, Native American Indians, Hawaiians, and Hispanics) when compared to Whites. However, the data set available was unable to account for socioeconomic or educational status.

Other variables that may contribute to confounding include antidepressant use, antidementia medications, previous psychiatric history, disorders such as trisomy 21, socio-economic status, and education level. While some of these variables are often controlled for with exclusion (such as trisomy 21 and previous psychiatric history), others cannot reasonably be excluded. Antidementia medications and antidepressant use can affect the prevalence of depressive symptoms but would be impractical to exclude from the study because a majority of patients with EOD and LOD are being treated with antidementia medications such as donepezil and memantine. Acetylcholinesterase inhibitors such as donepezil and rivastigmine have been shown to affect depression scores in patients with AD. Other studies examined did not account for medication use and may have been a potential limitation of those studies. A multivariate analysis to account for confounding variables such as medication use, will be performed for the primary outcome of this study.
2.4 Relevant Methodology

2.4.1 Study Design and Setting

The CSDD scale stipulates an interview of the caregiver of a patient alongside a brief interview of the patient for an accurate assessment. Given that patients with dementia are definitionally cognitively impaired and may not provide an accurate assessment on their own, a caregiver interview is needed to compare the results of the scale.\textsuperscript{14} If caregivers had a significant difference in the assessment of depressive symptoms in patients with EOD vs LOD, this could affect the outcome of the results. A 2018 cross-sectional study sought to measure the caregivers’ perspective about QOL (including depression) of patients with EOAD and LOAD.\textsuperscript{15} The study interviewed caregivers of 53 patients with EOAD and caregivers of 57 patients with LOAD. The purpose of the study was to assess if perspectives of caregivers’ assessments of QOL of patients with EOAD differ from caregivers’ assessments of QOL of patients with LOAD. The study found no significant difference in caregivers’ ratings of QOL in both groups (p = 0.540). The study examined patients with AD and did not include other types of dementia and therefore might not necessarily reflect similar results when generalized.

Existing studies that have examined depression in those with EOD compared to LOD have had varying geographical settings. We were unable to identify any studies that had participants from US memory clinics examining the relationship of depressive symptoms in EOD vs LOD. The major studies examined above that looked at this relationship, took place in The Netherlands, Norway, Denmark, Iceland, Portugal, and rural Canada, all of which may not be equivalent to results obtained with a comparable US population.\textsuperscript{1-3,6} However, the studies examined have primarily recruited patients from
memory centers because a high number of patients with dementia are treated at these centers.\textsuperscript{1-3,6} While dementia can be diagnosed outside of memory centers, patients will often be referred to memory centers for long-term management and care, centralizing patients with dementia into one location. Recruiting patients from memory centers is comparably easier and likely cheaper than recruiting patients from other settings, and makes sense to do so in this study.

At baselines, chi-squared tests are frequently in the studies examined used to compare categorical variables between EOD and LOD patients including race, sex, education level, marital status, etc., while independent sample \( t \)-tests are used to compare continuous variables such as age and disease duration. In order to test our primary dichotomous outcome, a chi-squared test can be used. To account for confounding variables, multiple logistic regression should additionally be performed for the primary outcome. Confounding can also be accounted for with exclusion criteria discussed above. When considering secondary outcome measures, such as age, sex, race, and education level, chi-squared tests can be used for categorical variables (e.g. education level, race, sex) and \( t \)-tests for continuous variables (e.g. age). Variables with a p-value of less than 0.05 are considered significant in all of the studies that we examined.

\subsection*{2.4.2 Primary and Secondary Outcomes}

Most of the studies reviewed above had primary outcomes of severity of neuropsychiatric symptoms or quality of life measures. When neuropsychiatric symptoms were used as a primary outcome, a measure of depressive symptoms was among the subset of symptoms reported. Other neuropsychiatric symptoms typically measured by
the NPI scale as a primary measure include aberrant motor behavior, agitation, anxiety, apathy, depression, disinhibition, eating changes, euphoria, hallucinations, irritability, and nighttime behavior. While the NPI scale measures both frequencies of symptoms and severity of symptoms, studies such as the Dutch study and Portuguese studies mentioned above have utilized the scale for the mere prevalence of symptoms.3,6,16

The studies examined rely on measures of depressive symptoms and do not account for major depressive episodes. There appears to be a paucity in whether major depressive episodes are related to the development of dementia or the prevalence of episodes in existing patients with dementia. In a systematic review of depression and dementia, it was shown that patients with several hospitalizations for depression had an increased risk of subsequently developing dementia.17 The CSDD has the advantage of being able to assess for probable major depressive episodes. The scale has 19 items, with a minimum score of 0 and a maximum score of 38. Probable major depressive episodes correspond to scores greater than 10, with definite major depressive episodes scoring greater than 18.14,18 While the CSDD can be used to assess for depressive episodes, existing studies such as the Nordic study above, have used the scale to assess for depressive symptoms using a discrete scale from 0-38, rather than a dichotomous measure of having a probable episode of depression vs not having an episode.1

Secondary outcomes in the various studies examined included age, years of education, sex, disease duration, patient medication use, a measure of cognitive function, and measures of dementia severity.1-3,6

Patient medication use, if measured, was frequently recorded in classifications of medications such as antipsychotics, antidepressants, benzodiazepines,
acetylcholinesterase inhibitors, and NMDA receptor antagonists. Medication use in one study was recorded and classified into categories based on therapeutic use (e.g. cardiovascular diseases; psychiatric diseases) but was not analyzed as a secondary outcome.1

Data on age, years of education, sex, and patient medications, are all appropriate measures to collect for baseline characteristics of the EOD and LOD arms of the study. Cognitive impairment is frequently measured as a secondary outcome with the Mini Mental State Examination (MMSE), while dementia severity has been measured by various scales, most commonly the Global Deterioration Scale (GDS). The MMSE and GDS have been shown to be validated for these purposes.19,20

Secondary outcomes this study will seek to examine are the presence of anxiety and presence of agitation, as these measures can be examined and recorded directly from the CSDD. The CSDD has 3 scores available for anxiety and agitation ranging from 0 to 2, with 0 being absent, 1 being mild or intermittent, and 2 being severe.14 Using chi-square analysis, EOD and LOD groups can be compared for anxiety and agitation scores. Agitation and anxiety have been examined as subsets of neuropsychiatric profile outcomes by some of the studies outlined above. The 2012 Dutch prospective cohort study found that anxiety was lower in EOAD patients (40.5%) compared with the LOAD group (55.9%) (OR = 0.40, 95% CI = 0.18–0.89, p = 0.025). However, the study did not find a significant difference when examining agitation between the two groups.3 A 2017 cross-sectional study found no statistically significant results of changes in anxiety or agitation scores in EOAD vs LOAD, though the study sought overall differences in
neuropsychiatric profile as a primary outcome and was not powered for analysis of anxiety or agitation.⁶

### 2.4.3 Study Populations

EOD is defined as dementia occurring before 65 years old, but there is no apparent minimum age, with some patients being diagnosed as early as their 4th decade of life.¹² The most common type of dementia occurring in the 30s is AD associated with Down Syndrome. As noted above, Down Syndrome is a potential confounder for the relationship between depressive episodes and dementia, which is why it is usually excluded in populations being studied. Studies examining patients with EOD vs LOD have dichotomized the two groups by date of diagnosis of dementia before and after 65 years old for EOD and LOD respectively. Few studies, however, have specified a time frame after the diagnosis date for the date of inclusion. While studies examined did not limit themselves to selecting patients with EOD shortly after diagnosis, most of the patients examined in the various studies in the EOD arm were in their 60s and 70s when enrolled, while most of the patients in the LOD arms were in their late 70s when enrolled.²,³,⁶

In the 2017 cross-sectional study out of Portugal, the average length of disease at baseline was 5.7 (2.3) years for EOAD, and the average age of participants at diagnosis was 64.5 (± 6.5, but not exceeding 65) (n = 35) years old in the EOAD group.⁶ The median age of the LOAD arm was 76.0 (± 3.5) (n = 35).⁶

In the 2012 Dutch prospective cohort study, the average length of disease at baseline was 5.8 ± 3.2 years for EOD, and the average age of participants at diagnosis
was 61.2 ± 4.9 (n = 98) years old in the EOD group. The median age of the LOD arm was 78.8 ± 5.9 (n = 123).3

In the 2018 Nordic cross-sectional study the median age of EOD patients was 59 years old (range of 44 to 64) (n = 61). However, participants over 65 years old were allowed to join the EOD arm if the date of diagnosis was prior to them turning 65 years old. The study did not specify the age at baseline of the participants. The median age of the LOD arm was 77 years (range of 65 to 94) (n = 272).2

Justification for inclusion of patients with EOD and LOD several years after diagnosis is likely because the researchers were not seeking depressive episodes prevalence after a diagnosis of dementia, but were rather seeking depressive symptom differences between the two groups in general with similar disease duration. The cut-off age of 65 between patients with EOD and LOD is viewed as an arbitrary and historical distinction rather than a physiological distinction, with the important caveat that patients with EOD have been shown to have worse outcomes than patients with LOD at similar disease durations.21,22 Due to this distinction, and that EOD patients comprise a much smaller percentage of patients than LOD patients, recruitment of EOD patients is easier if there is a preexisting pool of patients to recruit from, rather than waiting for new diagnoses to be made.

Participants tend to be excluded from studies when the participant cannot speak a specific language or sometimes if the participant is actively living in a nursing home. The 2012 Dutch prospective cohort study excluded patients living in a nursing home, which could be considered a limitation of the study that could decrease the number of participants with severe dementia. Patients with higher severity of disease are more likely
to be in nursing homes than those with milder dementia. The explanation for this is unclear, but it is possible that primary caregivers would be less likely to be present with patients to give informed consent.

2.4.4 Selection Criteria

Selection methods for participants vary across studies, but most stipulate that EOD patients recruited must have been diagnosed before the age of 65 to definitionally meet the criteria of early-onset dementia, while patients with LOD must have been diagnosed after the age of 65. However, many studies allowed for patients in the EOD arm to be older than 65 at the time of the study.\textsuperscript{2,23} Since EOD comprises a small number of total cases of dementia, most studies examined attempted to recruit most patients from local memory centers with a diagnosis of EOD. For the LOD arm, some studies such as the 2012 Dutch prospective cohort study and the 2018 multicenter Nordic cross-sectional study matched EOD patients with LOD patients from separate studies with similar baseline characteristics.\textsuperscript{1,3}

Since our study will seek newly-diagnosed patients (within 6 months of a diagnosis), patients selected to participate in the study will have to have been diagnosed within the past 6 months to be eligible. This stipulation is unique to our study and was not present in any of the prior studies examined, as they sought depressive symptom severity between EOD and LOD, while our study seeks to examine probable depressive episodes prevalence specifically after a new diagnosis of dementia.
2.4.5 Sample Size

Many of the studies above sought a primary outcome of neuropsychiatric outcomes or quality of life measures which while including depressive symptoms as a subset, did not have depressive episodes as a primary outcome and therefore were not powered properly for depressive symptoms alone and could not be used to determine a proper sample size. This may help explain why there is wide variability in results of depressive symptom prevalence between EOD and LOD groups measured in these studies. Important to note, however, is that our study seeks to determine probable major depressive episodes in EOD vs LOD, while the aforementioned studies included measures of prevalence of depressive symptomatology within their measures. This difference is important, as the studies above tend to relate depressive symptoms as a continuous variable rather than a dichotomous variable that would be present in our study. Nonetheless, we calculate with a 5% margin of error, a 95% confidence level, and a response distribution of 50% an estimated effective sample size of 92 in the EOD arm given a normal distribution, which is similar to several of the studies reviewed including one with 61 participants, 98 participants, and 88 participants. Some of the studies examined have much larger and much smaller population sizes examined. The Portuguese study mentioned included just 35 EOAD patients and was unable to find a statistically significant difference between depression/dysphoria of EOAD and LOAD groups, and was likely limited by their small sample size. The 2014 global cross-sectional analysis mentioned had a sample size of 614 patients with EOAD, though they came from an existing database of patients and sought different primary and secondary outcomes from this study. We estimated we can recruit around 120 EOD patients at the
Dorothy Adler Geriatric Assessment Center over a two-year period. Our sample size calculations can be found in Appendix B and further discussion can be found in chapter 3.8.

2.5 Conclusion

Multiple studies have examined the prevalence of depressive symptoms in patients with EOD vs patients with LOD, however, they have examined these symptoms as a secondary outcome while primary outcomes focused on neuropsychiatric profiles or quality of life measures. The studies examined did not seek the presence of depressive episodes but rather focused on if patients had any symptoms of depression, and they sought differences between the two groups multiple years after diagnosis. The studies have had conflicting results with some suggesting that depressive symptoms are more common in EOD patients, some suggesting the symptoms are more common in LOD patients, and some without statically significant results. Some studies examined did not control for confounding. In two of the major studies, the population with LOD that was utilized was recruited from separate studies. Lastly, the geographical location of the studies was broad, and all of the studies that examined depression in EOD vs LOD did not take place within the United States. In conclusion, our proposed cross-sectional study will fill significant research gaps by examining depressive episodes in patients with new-onset EOD vs patients with new-onset LOD, in an urban and suburban US setting, while controlling for common confounding variables.
References


Chapter 3: Study Methods

3.1 Study Design

We will perform a cross-sectional study comparing patients with early-onset dementia (EOD) to patients with late-onset dementia (LOD) at the Dorothy Adler Geriatric Assessment Center in New Haven, CT. All patients with a new diagnosis of dementia within the past 6 months of the day they are assessed, will be asked to enroll in the study provided they meet eligibility. Patients will be enrolled into the EOD group if their age is less than 65 years old at the time of diagnosis of dementia. Patients who are 65 or older at the time of diagnosis of dementia will be recruited into the LOD group.

Both groups will initially be given a baseline self-administered questionnaire to fill out with their caregivers (see Appendix A). The clinician will administer the Mini Mental State Examination (MMSE) and the Global Deterioration Scale (GDS) to the patient. The clinician will then administer the Cornell Scale for Depression in Dementia (CSDD) to the caregiver. The clinician will then interview the patient to see if there are any discrepancies with the questions administered in the CSDD. If discrepancies are noted, the caregiver will be interviewed again to clarify discrepancies. The data obtained from the questionnaires and measures will be analyzed for primary and secondary outcomes.

There are no interventions or follow-ups performed in this study. While blinding is not possible in this study, participant data will be kept confidential, and caregiver personal information will not be utilized by this study. A mock enrollment will take place with 4 participants prior to initiation of the study to assess the duration of time the study
will take, but it is estimated that from start to finish, the screening and completion of the measures will take approximately 45 minutes.

3.2 Study Population and Sampling

The study population will be obtained from patients at Dorothy Adler Geriatric Assessment Center which is a treatment center for dementia patients that is part of the Yale New Haven Health System located in New Haven, Connecticut, US. Patients with a diagnosis of dementia within the last 6 months of a visit to the Adler center will be asked to enroll provided they meet inclusion and exclusion criteria. Only English-speaking patients with an English-speaking caregiver will be asked to enroll due to translation difficulties. If there are patients or caregivers that are illiterate, the questionnaire provided at the beginning of the visit will be read aloud to the participant with a chaperone in the room to ensure accuracy.

The self-administered questionnaire provided will ask about baseline characteristics of the patient including details about age, race, sex, type of dementia, years of education, and select medications including anti-dementia, anti-depressant, and antipsychotic medications. A sample questionnaire is available in Appendix A.

3.3 Inclusion and Exclusion Criteria

In order for patients to be included in the study, they must meet strict eligibility criteria. Inclusion criteria include a diagnosis of dementia made within the past 6 months of enrollment date. Exclusion criteria include a lack of informed consent. Due to cognitive impairment caused by dementia, patients with dementia are unable to have
informed consent singularly and require a caregiver to have informed consent. Both patients and caregivers will be asked to consent to the trial, and if either does not consent, they will not be included. Other exclusion criteria include dementia caused by Down’s syndrome, HIV, Huntington’s disease, Alcohol-related dementia, and traumatic brain injury (TBI). The exact type of dementia does not have to be known to participate in the study so long as these causes of dementia are excluded and the patient has a diagnosis of dementia. Patients with comorbid psychiatric disorders such as bipolar or schizoaffective disorder will be excluded from this study. Patients with major and minor depressive disorders, however, will be permitted to participate. Lastly, patients and caregivers must be able to speak English in order to participate in the study.

**Table 1. Eligibility Criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of dementia within the past 6 months</td>
<td>Lack of informed consent</td>
</tr>
<tr>
<td></td>
<td>Dementia caused by Down’s syndrome, HIV, Huntington’s disease, Alcohol-related dementia, TBI</td>
</tr>
<tr>
<td></td>
<td>Bipolar Disorder and other psychiatric disorders (major and minor depression are exceptions)</td>
</tr>
<tr>
<td></td>
<td>Non-English-speaking patient or caregiver</td>
</tr>
</tbody>
</table>

**3.4 Recruitment**

Since patients with dementia are cognitively impaired and thus have impaired decision-making capacity, both the patient and an accompanying caregiver will be required to consent in order to participate in the study. The caregiver present must provide permission for the patient to participate in the study. A research assistant or provider will explain the study and consent process and allow for any questions, prior to
the patient and caregiver providing consent. The interview will require patients and caregivers to speak English. For patients that are unable to read, instructions and consent information will be read aloud with a chaperone to ensure understanding and that all information provided is accurate before obtaining consent.

A self-administered questionnaire will then be given to the patient and caregiver to fill out together, asking about age, race, sex, type of dementia, years of education, comorbid psychiatric conditions, and select medications. The questionnaire can be found in Appendix A below. After the questionnaire is filled out, it will be briefly screened for exclusionary criteria by the research assistant or provider. If the patient does not meet the eligibility criteria listed above, they will be thanked for their time and informed they do not qualify for participation in the study and will continue with their regular appointment.

There will be no financial incentive to participate in this study. Patients who wish to enroll will be provided written information about the trial and provided resources on depression, regardless of their outcomes. Potential benefits of this study include free depression screening for patients and information on resources available for the treatment of depression.

3.5 Subject Protection and Confidentiality

Prior to initiation of the study, we will seek approval from the Yale Human Investigation Committee and Institutional Review Board (IRB) per IRB Policy 100. Given that the population of this study has a diagnosis of dementia and may be more vulnerable than a non-cognitively impaired population, there are additional safeguards we will meet to ensure subject protection. We will be required to follow IRB Policy 340:
Participation of Individuals with Impaired Consent. All research personnel involved in interacting with the research participants or data will complete human subjects protection training and Health Insurance Portability and Accountability Act (HIPAA) training prior to seeking IRB approval.

Every patient being considered for enrollment will be informed about the study by research personnel or a trained clinician and will include information about the study design and purpose, potential risks and benefits of the study, and provided time for questions prior to consenting. The caregiver must be a legally authorized representative or a surrogate such as a next of kin, spouse, parent, child, or sibling. The caregiver is required to give permission on behalf of the patient and will receive the same information prior to consent. An example of a consent form is provided in Appendix C. As this is a cross-sectional study with no interventions, there is no physical risk to participants enrolled in this study. The only potential risk is loss of confidentiality, which strong efforts will be made to avoid. The potential benefits of the study are outlined above but primarily include free depression screening. Any patient or surrogate that does not agree to the study parameters or decides they do not wish to participate will not be enrolled. Patients and caregivers will also be informed that they have the right to revoke their decision to participate in the study at any time and this will not be held against them for future care provided. If the patient or caregiver wishes to cease participation during a screening of the trial, the screening will be stopped immediately, and the patient will be removed from the study and thanked for their time.

Any data recorded from this study including patient identifiers and Protected Health Information (PHI) will be stored securely electronically with password protection.
and encryption and will be only accessible by those involved in conducting the study including the principal investigator (PI) and overseeing faculty. Any non-electronic PHI will be stored securely in a locked cabinet on-site and will be shredded upon completion of the study. Any patient information will be deidentified as soon as feasibly possible. Upon completion of the study, any further PHI will be disposed of in a secure manner. There are no financial incentives or conflicts of interest identified in this study.

3.6 Study Variables and Measures

3.6.1 Primary and Secondary Outcomes

The primary dependent variable is the overall CSDD score. Secondary dependent variables include individual measure scores taken from the CSDD for anxiety and for agitation. The CSDD score for the primary outcome will be a dichotomous outcome with the number of scores greater than 10 representing a probable major depressive episode and scores 10 or less representing no probable major depressive episode. We believe that there will be a statistically different prevalence ratio of probable major depressive episodes between the patients with EOD and the patients with LOD.

Secondary outcomes of agitation or anxiety include a discrete score from 0 to 2 of the respective individual measures of the CSDD, with 0 being absent, 1 being mild or intermittent, and 2 being severe.

3.6.2 Potential Confounding

Potential confounding variables identified in this study that will be controlled for by exclusion include the presence of Down Syndrome, traumatic brain injuries, HIV,
Huntington’s disease, alcohol-related dementia, bipolar disorder, and diagnosed psychiatric disorders (excluding major and minor depression diagnoses). These conditions will be identified by the self-administered questionnaire provided. Cognitive impairment scores as measured by MMSE, dementia severity as measured by GDS scores, and select medication use including antidepressants, antidementia medications, and antipsychotic medications will be controlled for using a multivariate analysis.

3.7 Data Collection

Initially, after enrollment, patients will be given a self-administered questionnaire to fill out with their caregiver which collects data about baseline characteristics including age, race, and education level, as well as, select medication usage (anti-dementia, anti-depressant, and anti-psychotic medications), type of dementia, and history of psychiatric conditions. Some of the information included such as type of dementia and history of psychiatric conditions may be used to exclude patients from the study based on the eligibility criteria listed above. An example of the questionnaire can be found in Appendix A.

After screening for exclusion criteria, those who qualify for participation will be given the MMSE, by a trained clinician, which assesses cognitive function. The MMSE has a total possible score of 30, with lower scores representing higher levels of cognitive impairment. The MMSE can be found in Appendix A.

The GDS will be administered by a trained clinician after the MMSE. Results of the GDS will give patients a score from 1 to 7 classifying the severity of the patient’s dementia. The GDS can be found in Appendix A.
Finally, the CSDD will be administered to the caregiver. If there is a discrepancy between the interviewer’s impression and the caregiver’s response, the interviewer will ask the caregiver again to clarify. The CSDD has a minimum score of 0 and a maximum score of 38. The CSDD can be found in Appendix A. The CSDD will be the last measure assessed during this cross-sectional study, after which the patient and caregiver will be thanked for their time.

**Figure 1: Study Protocol**
3.8 Sample Size Calculation

Due to the rarity of EOD, patients enrolled in the EOD arm will be the limiting factor for sample size. Several assumptions must be made to calculate a proposed sample size given the difficulty of estimating the number of patients diagnosed with EOD each year. The incidence of AD has been estimated to be approximately 910,000 people in the US each year. Given Alzheimer’s makes up the majority of dementia and to be conservative, there is an incidence of approximately 1 million people in the US diagnosed with dementia each year. Given the population proportion of Connecticut compared to the US as a whole, we estimated approximately 11,000 patients are diagnosed with dementia each year in Connecticut. Given that approximately 5.5% of patients with dementia are diagnosed before the age of 65, this reduces our number to 605 people. Assuming that only 10% of the state population of these are diagnosed and referred to the Adler Center as opposed to another institution, this lowers our sample to approximately 60 people per year that are diagnosed with EOD that can be recruited. Given a two-year recruitment period, we estimate that up to 120 patients with EOD can be recruited for our study. With a population of 120, a 5% margin of error, a 95% confidence level, and a response distribution of a conservative 50%, we estimate an effective sample size of 92, given a normal distribution. Assuming 20% of patients with EOD are unable to be recruited or are not eligible for our study, this leaves approximately 96 patients with EOD that can be recruited. A breakdown of the sample size calculation can be found in Appendix B.
3.9 Statistical Analysis

The primary outcome of CSDD scores will be initially tested with a bivariate analysis using a chi-squared test. A multiple logistic regression test will be performed for multivariate analysis to assess the primary outcome while accounting for confounding variables, including MMSE score, GDS score, and select medication use.

For analysis of baseline characteristics, a chi-squared analysis will be performed for categorical and ordinal variables including education level, race, and sex. Continuous variables such as age and years of education will be assessed with $t$-tests.

Secondary outcomes of agitation and anxiety are ordinal variables with results ranging from 0 to 2. These outcomes will be tested with a chi-squared analysis.

3.10 Timeline and Resources

Pending IRB approval, enrollment in this study will take place over a timeframe of 24 months. This is to ensure that the calculated sample size is met for the EOD arm of the study as discussed above. After the enrollment period finishes, data analysis will be performed and is expected to take approximately 2 months. The length of time of data analysis was not accounted for in the 24-month enrollment period.

The principal investigator for this research study will be Alex Hauptli, BSc, PA-SII. Students are permitted to be the PI if they are under the oversight of a faculty advisor who meets the qualifications of a PI including those that are employed full-time by Yale and hold the position of assistant professor, associate professor, professor, research scientist/scholar, or senior research scientist/scholar. Study oversight will be performed by the PI and faculty advisor. Additional research personnel needed for our study, include
1 or 2 research assistants, depending on demand, to assist with consenting, handing out the questionnaires, and data analysis. Clinicians at the Dorothy Adler Geriatric Assessment Center who are willing to engage in conducting this study will need to be trained to administer the MMSE, GDS, and CSDD, as well as have the required human subjects protection training and HIPAA training.

The CSDD is copyrighted and permission will need to be obtained to use the scale in this study prior to submission to the IRB. Permission will be requested in writing from George Alexopoulos, MD at New York Hospital – Cornell Medical Center, Westchester Division, 21 Bloomingdale Road, White Plains, NY 10605, or can be requested in writing from Elsevier Science, Subsidiary Right Dept., P.O. Box 800, Oxford OX5 1DX, United Kingdom. If we are unable to obtain permission to use the CSDD, the study design will have to be altered to use another available scale such as the Geriatric Depression Scale which is available in the public domain but would have the limitation of not being validated for patients under the age of 65.

Additional resources required for our study include a room in the Adler Center in which to administer and conduct the MMSE, GDS, and CSDD, as well as permission to conduct the study at the Adler Center. Office space will be needed for data analysis and review, though this does not have to be located at the Adler center.

References

Chapter 4: Conclusion

4.1 Advantages and Disadvantages

Our proposed study has several major advantages over existing studies. Firstly, our study examines patients with dementia within 6 months of a diagnosis for probable major depression episodes. Existing studies have examined patients for possible depressive symptoms years after a diagnosis. Additionally, our study would examine depression in an urban and suburban US population with EOD and LOD, which to our knowledge has not been examined in the last 10 years and could provide valuable data about the two groups.

We believe our study is both feasible and ethical, presenting with no physical risks to patients. Benefits of this study include screening for depression and being provided with resources for the treatment of depression. Since depression and dementia are highly correlated, we feel this benefit outweighs any potential risk.¹

Our study does possess some limitations. Exclusion of patients with TBI, HIV, Down’s syndrome, Huntington’s disease, Alcohol-related dementia, bipolar, and those that do not speak English limits the generalizability of our study. While this study aims to examine patients within 6 months of a diagnosis of dementia for probable depressive episodes, the CSDD assesses for probable major depressive episodes during the week prior to the interview, limiting the number of probable major depressive episodes able to be identified at a similar time point.²

While attempting to control for cognitive impairment severity with the MMSE, the tool relies heavily on verbal response and reading and writing, so patients with impaired vision or who are illegible would have worse cognitive impairment scores than
otherwise indicated. Impaired vision becomes increasingly prevalent with age, and the patients in the LOD group may have skewed results as a result.³

While dementia begins at the onset of cognitive impairment, there are frequent delays in diagnosis.⁴ It is possible that some patients diagnosed with LOD may have had a delayed diagnosis and should have been diagnosed with EOD if symptoms began prior to the age of 65. Unfortunately, without better early detection strategies this may always be a limiting factor.

We conservatively estimate that 20% of eligible patients with EOD will not qualify or will refuse to participate in this study, leaving approximately 96 patients with EOD to participate which exceeds our estimated sample size of 92 patients. However, it is possible that this estimate of 20% is too low, due to the fact that the study takes approximately 45 minutes, more patients may choose to defer participation due to time constraints which might limit the significance of our results.

Given the scarcity of information about disease incidence in EOD, several assumptions were made estimating the number of patients diagnosed with EOD that could be seen at the Adler Center in the 24-month period.⁵ Our estimate of 120 patients with a diagnosis of EOD may be inaccurate by a large degree.

4.2 Clinical and Public Health Significance

This study will increase understanding of depressive episodes in those with EOD compared to those with LOD. While much research has been done associating depression and dementia, few studies look at those with EOD compared to their older counterparts. This research seeks to fill this ongoing literature gap. Many existing depression
screenings performed on patients with dementia utilize the geriatric depression scale which is not validated for patients with EOD given their age and may be inferior to the CSDD. If this study has significant results, it could potentially increase routine depression screenings with the CSDD scale in patients with EOD and in patients with LOD. Additionally, significant results may demonstrate a further need for interventional research into better treatments of depression in patients with EOD and LOD.

References

APPENDIX

Appendix A: Data Collection Scales & Assessments

Self-Administered Questionnaire Sample

This questionnaire will ask you questions about your health history and medication use. Please complete the questionnaire with your caregiver.

Patient Name: ___________________________  Today’s Date ________________

Relationship of caregiver to patient: ___________________________

Date of Birth: __________  Current Age: _____

Please indicate how you identify yourself:

☐ American Indian or Alaskan Native
☐ Asian
☐ Black or African American
☐ Native Hawaiian
☐ White
☐ Other: _______________

Are you Hispanic or Latino?

☐ YES
☐ NO

What is your highest level of education?

☐ Less than High School
☐ Some High School
☐ High School Graduate or Equivalent
☐ Some College (No degree)
☐ Associate Degree
☐ Bachelor’s Degree
☐ Master’s Degree
☐ Doctorate Degree

Were you diagnosed with dementia within the past 6 months?

☐ YES
☐ NO

Which type of dementia have you been diagnosed with?

☐ Alzheimer’s Disease / Dementia
☐ Frontotemporal Lobe Dementia
☐ Lewy Body Dementia
☐ Vascular Dementia
☐ Unknown
☐ Other: _______________________

Have you ever been diagnosed with Major or Minor Depressive disorders?

☐ YES
☐ NO

Continued on Reverse Side
Have you ever been diagnosed with bipolar disorder, schizophrenia, or any other psychiatric conditions?

☐ YES
☐ NO
If YES, which conditions?

Do you take any medications for dementia?

☐ YES
☐ NO
If YES, which medications?

Do you take any medications for depression?

☐ YES
☐ NO
If YES, which medications?

Do you take any antipsychotic medications?

☐ YES
☐ NO
If YES, which medications?
Cornell Scale for Depression in Dementia (CSDD)

### Screening Tool: Cornell Scale for Depression in Dementia (CSDD)

**Scoring System:**
- a = unable to evaluate
- 0 = absent
- 1 = mild or intermittent
- 2 = severe

Ratings should be based on symptoms and signs occurring during the week prior to interview. No score should be given if symptoms result from physical disability or illness.

#### A. Mood-Related Signs

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anxiety  anxious expression, ruminations, worrying</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>2. Sadness  sad expression, sad voice, tearfulness</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>3. Lack of reactivity to pleasant events</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>4. Irritability  easily annoyed, short-tempered</td>
<td>a 0 1 2</td>
</tr>
</tbody>
</table>

#### B. Behavioral Disturbance

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Agitation  restlessness, handwringing, hairpulling</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>2. Retardation  slow movements, slow speech, slow reactions</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>3. Multiple physical complaints (score 0 if GI symptoms only)</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>4. Loss of interest  less involved in usual activities (score only if change occurred acutely, i.e., in less than 1 month)</td>
<td>a 0 1 2</td>
</tr>
</tbody>
</table>

#### C. Physical Signs

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Appetite loss  eating less than usual</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>2. Weight loss  score 2 if greater than 5 lb. in one month</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>3. Lack of energy  fatigues easily, unable to sustain activities (score only if change occurred acutely, i.e., in less than 1 month)</td>
<td>a 0 1 2</td>
</tr>
</tbody>
</table>

#### D. Cyclic Functions

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diurnal variation of mood symptoms worse in the morning</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>2. Difficulty falling asleep later than usual for this individual</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>3. Multiple awakenings during sleep earlier than usual for this individual</td>
<td>a 0 1 2</td>
</tr>
</tbody>
</table>

#### E. Ideational Disturbance

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Suicide  feels life is not worth living, has suicidal wishes or makes suicide attempt</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>2. Poor self-esteem  self-blame, self-deprecation, feelings of failure</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>3. Pessimism anticipation of the worst</td>
<td>a 0 1 2</td>
</tr>
<tr>
<td>4. Mood-congruent delusions delusions of poverty, illness or loss</td>
<td>a 0 1 2</td>
</tr>
</tbody>
</table>

**Scoring:**
- A score >10 probably major depressive episode
- A score >18 definite major depressive episode
### Global Deterioration Scale (GDS)

<table>
<thead>
<tr>
<th>Level</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No subjective complaints of memory deficit. No memory deficit evident on clinical interview.</td>
</tr>
<tr>
<td>2</td>
<td>Subjective complaints of memory deficit, most frequently in following areas: (a) forgetting where one has placed familiar objects; (b) forgetting names one formerly knew well. No objective evidence of memory deficit on clinical interview. No objective deficits in employment or social situations. Appropriate concern with respect to symptomatology.</td>
</tr>
<tr>
<td>3</td>
<td>Earliest clear-cut deficits. Manifestations in more than one of the following areas: (a) patient may have gotten lost when traveling to an unfamiliar location; (b) co-workers become aware of patient's relatively poor performance; (c) word and name finding deficit becomes evident to intimates; (d) patient may read a passage or a book and retain relatively little material; (e) patient may demonstrate decreased facility in remembering names upon introduction to new people; (f) patient may have lost or misplaced an object of value; (g) concentration deficit may be evident on clinical testing. Objective evidence of memory deficit obtained only with an intensive interview. Decreased performance in demanding employment and social settings. Denial begins to become manifest in patient. Mild to moderate anxiety accompanies symptoms.</td>
</tr>
<tr>
<td>4</td>
<td>Clear-cut deficit on careful clinical interview. Deficit manifest in following areas: (a) decreased knowledge of current and recent events; (b) may exhibit some deficit in memory of ones personal history; (c) concentration deficit elicited on serial subtractions; (d) decreased ability to travel, handle finances, etc. Frequently no deficit in following areas: (a) orientation to time and place; (b) recognition of familiar persons and faces; (c) ability to travel to familiar locations. Inability to perform complex tasks. Denial is dominant defense mechanism. Flattening of affect and withdrawal from challenging situations frequently occur.</td>
</tr>
<tr>
<td>5</td>
<td>Patient can no longer survive without some assistance. Patient is unable during interview to recall a major relevant aspect of their current lives, e.g., an address or telephone number of many years, the names of close family members (such as grandchildren), the name of the high school or college from which they graduated. Frequently some disorientation to time (date, day of week, season, etc.) or to place. An educated person may have difficulty counting back from 40 by 4s or from 20 by 2s. Persons at this stage retain knowledge of many major facts regarding themselves and others. They invariably know their own names and generally know their spouses' and children's names. They require no assistance with toileting and eating, but may have some difficulty choosing the proper clothing to wear.</td>
</tr>
<tr>
<td>6</td>
<td>May occasionally forget the name of the spouse upon whom they are entirely dependent for survival. Will be largely unaware of all recent events and experiences in their lives. Retain some knowledge of their past lives but this is very sketchy. Generally unaware of their surroundings, the year, the season, etc. May have difficulty counting from 10, both backward and, sometimes, forward. Will require some assistance with activities of daily living, e.g., may become incontinent, will require travel assistance but occasionally will be able to travel to familiar locations. Diurnal rhythm frequently disturbed. Almost always recall their own name. [Continued on next page]</td>
</tr>
</tbody>
</table>
Frequently continue to be able to distinguish familiar from unfamiliar persons in their environment. Personality and emotional changes occur. These are quite variable and include: (a) delusional behavior, e.g., patients may accuse their spouse of being an imposter, may talk to imaginary figures in the environment, or to their own reflection in the mirror; (b) obsessive symptoms, e.g., person may continually repeat simple cleaning activities; (c) anxiety symptoms, agitation, and even previously nonexistent violent behavior may occur; (d) cognitive abulia, i.e., loss of willpower because an individual cannot carry a thought long enough to determine a purposeful course of action.

<table>
<thead>
<tr>
<th>7</th>
<th>Very severe cognitive decline (Severe Dementia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All verbal abilities are lost over the course of this stage. Frequently there is no speech at all -only unintelligible utterances and rare emergence of seemingly forgotten words and phrases. Incontinent of urine, requires assistance toileting and feeding. Basic psychomotor skills, e.g., ability to walk, are lost with the progression of this stage. The brain appears to no longer be able to tell the body what to do. Generalized rigidity and developmental neurologic reflexes are frequently present.</td>
<td></td>
</tr>
</tbody>
</table>
**Mini-Mental State Examination (MMSE)**

Instructions: Ask the questions in the order listed.
Score one point for each correct response within each question or activity.

<table>
<thead>
<tr>
<th>Maximum Score</th>
<th>Patient's Score</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>“What is the year? Season? Date? Day of the week? Month?”</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“Where are we now? State? County? Town/city? Hospital? Floor?”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient’s response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials:</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“I would like you to count backward from 100 by sevens.” (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: “Spell WORLD backwards.” (D-L-R-O-W)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Earlier I told you the names of three things. Can you tell me what those were?”</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Repeat the phrase: ‘No ifs, ands, or buts.’”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Take the paper in your right hand, fold it in half, and put it on the floor.” (The examiner gives the patient a piece of blank paper)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please read this and do what it says.” (Written instruction is “Close your eyes.”)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please copy this picture.” (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>30</th>
<th>TOTAL</th>
</tr>
</thead>
</table>

**Patient’s Name:** ___________________________  **Date:** ___________________________
Appendix B: Sample Size Calculation

Sample size calculation assuming an EOD-limited population of 120, with a 5% margin of error, a 95% confidence level, and a response distribution of 50%. Assume normal distribution.

\[
n' = \frac{n}{1 + \frac{z^2 \times \hat{p}(1 - \hat{p})}{\varepsilon^2 N}}
\]

\[
n = \frac{z^2 \times \hat{p}(1 - \hat{p})}{\varepsilon^2}
\]

\[
n' = \frac{z^2 \times \hat{p}(1 - \hat{p})}{1 + \frac{z^2 \times \hat{p}(1 - \hat{p})}{\varepsilon^2 N}}
\]

\[
n' = \frac{1.96^2 \times 0.5(1 - 0.5)}{0.05^2(120)}
\]

\[
n' = \frac{384.16}{4.2013} = 91.438
\]

\[
\approx 92 \text{ patients required per arm}
\]

There are an estimated 120 patients in the population we are able to recruit over a 24-month period, assuming 20% are non-eligible to participate, that leaves 96 patients in the EOD arm which is 4 more than required to achieve our confidence level.
Appendix C: Sample Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT  
200 FR. 1 (2016-2)  
and  
IRB Policy 340 Participation of Individuals with Impaired Consent Capacity

Study Title: Depressive Episodes in Patients with Newly-Diagnosed Early-Onset Dementia vs Late-Onset Dementia  
Principal Investigator: Alex Hauptli, BSc, PA-SII  
Affiliation: Yale University School of Medicine and Yale New Haven Health System

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look for potential depressive episodes in patients with a new-diagnosis of dementia. You have been asked to participate because you have a diagnosis of dementia within the past 6 months.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the screenings that will be performed, any risks, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study, you will be asked to fill out a questionnaire (with your caregiver) and be interviewed by a medical provider. You will be asked questions about your mental status and any memory loss. You will be asked to draw a picture, follow simple instructions, and repeat phrases. You will also be asked questions related to mood, overall health and depression.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Risks and Inconveniences

There are no physical risks associated with this study. However, some questions may make you uncomfortable and there is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.
If you agree to this study, the screenings are estimated to take approximately 45 minutes.

**Benefits**

This study is performed at no cost to you. If you choose to participate, you will receive a free depression screening from a medical provider.

Regardless of whether you choose to participate, information on resources available for the treatment of depression will be made available to you at no cost.

**Confidentiality**

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Any data recorded from this study including patient identifiers and Protected Health Information (PHI) will be stored securely electronically with password protection and encryption and will be only accessible by those involved in conducting the study including the principal investigator and overseeing faculty. Any non-electronic PHI will be stored securely in a locked cabinet on site, and will be shredded upon completion of the study. Any patient information will be deidentified as soon as feasibly possible. Upon completion of the study any further PHI will be disposed of in a secure manner. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

**Voluntary Participation and Withdrawal**

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.
Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. If during the middle of a screening you wish to withdraw, simply inform the provider or another member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. If you are identified to have conditions such as HIV, alcohol-related dementia, Huntington’s disease, a traumatic brain injury, bipolar disorder or other psychiatric diagnoses (with the exception of diagnosed depression).

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or Yale-New Haven Hospital, Dorothy Adler Geriatric Assessment Center.

When you withdraw from the study, no new health information identifying you will be gathered after that moment. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.
Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researches to use (and give out) information about myself for the purpose described in the form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject: __________________________

Signature: _______________________________

Relationship of Caregiver: __________________________

Surrogate / Next of Kin / Legally Authorized Representative Signature:

__________________________________________

Date: ______________________________

Signature of Principal Investigator or Person Obtaining Consent  Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Alex Hauptli by email at Alex.Hauptli@Yale.edu

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
Bibliography


