

**National Institute of Mental Health Depression of Alzheimer
Disease:**
**Assessment and Diagnostic Validity Studies using Depression Scales
Developed for Older Adults**

by

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Abstract

The Lancet published a large multicenter randomized controlled clinical trial of noradrenergic and specific serotonergic antidepressant (NSSA) and selective serotonin re-uptake inhibitors (SSRI) for depression in Alzheimer's disease (AD) suggesting that these compounds have no clinical benefit [Banerjee et al 2011]. We felt that it might be premature to suggest that the use of all antidepressant treatments is ineffective [Sepehry et al 2012]. In response, we ran a meta-analysis examining the evidence for the use of SSRIs for treatment of depression co-occurring with AD [Sepehry et al 2012, see Appendix N]. This study suggested that treatment effects are potentially assessment dependent, and provided the motivation for the current examination of depression diagnostic criteria and assessment/screening scales for AD. A literature search showed that Provisional Diagnostic Criteria for depression of AD (PDC-dAD) was proposed to diagnose depression in AD. Their validity has not been established, yet they have been used in epidemiological studies and clinical trials. Likewise, no study examined short and easy to use screening measures with comparable collateral version's validity and utility for use with the PDC-dAD. Hence, I set these as my goals: to examine the validity-evidence of the PDC-dAD followed by simultaneous examination of the reliability (internal consistency), utility, and validity (content, construct, and concurrent) of screening measures already validated for use with older adults, for use with the PDC-dAD. Thus, the literature around depression in older adults and in AD was reviewed to improve understanding of the importance of investigating depression and its diagnostic/assessment approaches. Briefly, the result of the validity studies showed that, first, the PDC-dAD are the best that exist to date for diagnosing depression in AD; however it needs optimization. Second, screening measures developed for depression in older adults, including the collateral version, are psychometrically acceptable (valid and reliable) allowing for adequate screening of mild to mildly-moderate AD for dAD; however, the collateral version was the most valid given its psychometric properties, particularly, positive predictive value,

specificity, and clinical accuracy for use with the PDC. Hence, recommendations are made for the use of the screening scales with the PDC and for future research.

Preface

If everyone is thinking alike then somebody isn't thinking.

George S. Patton

All of the work presented henceforth was accomplished at the University of British Columbia (UBC) Faculty of Medicine, Division of Neurology and at the UBC Hospital Clinic for Alzheimer Disease and Related Disorders (CARD).

Study 1 (Chapter 3) — A version of this material has been peer-reviewed and resubmitted for publication. As lead investigator, I was responsible for all major area of concept formation, data collection and analysis, as well as dissertation composition. Drs. Hsiung and Lee provided input into various sections of the dissertation, including overall revisions. Drs. Beattie and Feldman provided input into various sections of the dissertation, including overall revisions and editing for content. Dr. Jacova supervised the project, helped in the interpretation of the data, revised the dissertation and edited for content.

Study 2 (Chapter 4) — I was the primary investigator for this observational study. Dr. Jacova was the co-investigator and supervisory author. Drs. Beattie, Feldman, Hsiung, and Lee were involved in the early stages of concept formation, contributed to data collection and dissertation edits. Drs. Foti and Genge contributed to data collection and dissertation edits.

The UBC Research Ethics Board approved this project (REB: H11-01598).

Study 3 (Chapter 5) —I was the primary investigator for this content validity study. Drs. Jacova and Hubley were the supervisory authors of the work, and also helped in interpretation of data and dissertation revision. Drs. Hubley and Lee helped in the formation of the survey. Drs. Lee and Hsiung were involved in data collection and dissertation edits. The manuscript for this study has been completed and now is pending for submission.

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List of Abbreviations

3MS: Modified Mini-Mental State

5-HT: Serotonin

A

ACh: Acetylcholine

AD: Alzheimer's Disease

APA: American Psychiatric Association

APoE: Apolipoprotein E

AQ-D: Anosognosia Questionnaire-Dementia

AUC: Area Under the Curve

B

BA: Brodmann's Area

BDI: Beck Depression Inventory

C

CAMDEX: Cambridge Examination of Mental Disorders

CCCDTD: Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

CERAD-K: Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet-Korean version

CES-D: Center for Epidemiologic Studies Depression Scale

CI: Confidence Interval

CIE: Canberra Interview for the Elderly DSM-IV-TR

CIHR: Canadian Institute of Health Research

CIND: Cognitive Impairment No Dementia

CMA: Comprehensive Meta-analysis

CNS: Central Nervous System

CRF: Case Report Form

CSDD: Cornell Scale for Depression in Dementia

CSF: Cerebrospinal Fluid

CVI: Content Validity Index

CVLT: California Verbal Learning Test

D

DA: Dopamine

DIADS: Depression in Alzheimer's Disease Study

DMAS: Dementia Mood Assessment Scale

DMTS: Delayed Matching To Sample

DSM: Diagnostic and Statistical Manual of Mental Disorders

E

EC: Entorhinal Cortex

EEG: Electroencephalography

EMBASE: Excerpta Medica dataBASE

ER: Event Rate

F

F: Female

FDA: Food and Drug Administration

FDG-PET: 18-Fluoro-deoxyglucose positron emission tomography

FRCPC: Fellow of the Royal College of Physician of Canada

FRONTIER: Facing Rural Obstacles to Healthcare Now Through Intervention, Education & Research

G

GABA: Gamma-Aminobutyric Acid

GDS-30: Geriatric Depression Scale-30 items

GDSIF-30: Geriatric Depression Scale for Informant-30 items

H

HAMD/HDRS/HAM-D: Hamilton rating scale for Depression

HDS-OA: Hubley Depression scale for Older Adults

HPA/HTPA: Hypothalamic-Pituitary-Adrenal axis

HTA-SADD: Health Technology Assessment-Study of the use of antidepressants for depression in dementia

I

I-CVI: Item-level Content validity index

ICD: International Classification of Diseases

ISTAART: International Society to Advance Alzheimer's Research and Treatment

IWG: International Working Group

M

MADRS: Montgomery–Åsberg Depression Rating Scale

Max: Maximum

MCI: Mild Cognitive Impairment

MD: Medical Doctor

MDD: Major Depressive Disorder

MDS: Minimum Data Set

Min: Minimum

MMSE: Mini–Mental State Examination

MoCA: Montreal Cognitive Assessment

MOOSE: Meta-analysis Of Observational Studies in Epidemiology

MWU: Mann Whitney-U

N

n: Sample size (individual patient)

N: Sample size (individual study)

NA: Not Applicable

NCD: Neurocognitive Disorders

NE: Norepinephrine

NIA-AA: National Institute on Aging–Alzheimer's Association

NIMH: National Institute of Mental Health

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NPI: Neuropsychiatric Inventory

NPV: Negative Predictive Value

NR: Not Reported

NRI: Norepinephrine Reuptake Inhibitors

NRS: Neurobehavioral Rating Scale

NS: Non-Significant

O

OR: Odd Ratio

P

PDC-dAD: Provisional Diagnostic Criteria for depression of Alzheimer's Disease

PDC-: PDC negatives

PDC+: PDC positives

PHQ: Patient Health Questionnaire

PP: Point Prevalence

PPV: Positive Predictive Value

PRISMA: Preferred reporting items for systematic reviews and meta-analyses

PubMed: National Library of Medicine's collection database

Q

QOL: Quality of Life

R

RA: Research Assistant

RAVLT: Rey Auditory Verbal Learning Test

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

rbp: by partial relationship

RCT: Randomized Controlled Trial

RDC: Research Diagnostic Criteria

REB: Research Ethics Board

ROC: Receiver Operating Characteristic Curve

S

SCID: Structural Clinical Interview for Depression

SD: Standard Deviation

Se: Sensitivity

SE: Standard Error

Sec: Seconds

SME: Subject Matter Experts

SNRI: Serotonin–norepinephrine Reuptake Inhibitors

Sp: Specificity

SSRI: Selective Serotonin Re-uptake Inhibitors or Serotonin-Specific Reuptake Inhibitor

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

U

UBCH-CARD: University of British Columbia Hospital-Clinic for Alzheimer Disease and Related Disorders

V

Ver: Version

W

WAIS-R: Wechsler Adult Intelligence Scale-revised

WCST: Wisconsin Card Sort Test

WHO: World Health Organization

WMS: Wechsler Memory Scale

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Dedication

Keep your dreams alive. Understand that to achieve anything greater than expected requires faith and belief in your abilities, vision, determination, dedication, and above all hard work.

Remember that all things are possible for those who believe.

To the people with shattered minds....and lives

Introduction

Depression is a devastating disorder. Alzheimer's Disease (AD)¹ is equally devastating. It is nearly impossible to imagine the emotional burden of those that suffer from both of these conditions. There is still no cure for AD, but depression can be treated. Recognizing that Alzheimer's patients can also suffer from depression provides potentially important avenues for treatments to ease this suffering. Thus the overall aim of this dissertation is to address the unique challenges of assessing depression in patients with AD, with the hope of facilitating the recognition of this disorder.

Research into depression in older adults has been rapidly expanding recently. This is due to many factors including the heterogeneity in classifying depression, the multiple risk factors and numerous hypothesized neurobiological links, the range of neuropsychological as well as behavioral symptoms presented, and the various assessment approaches. Also, there has been heightened interest in this field due to the substantial impact that depression has on the individuals, family members and care providers in our society. There are many challenges in the field, particularly concerning the recognition, assessment, and diagnosis of depression in older adults, specifically for those suffering from AD. When present, depression complicates recognition and management of the AD symptoms, yet little work has been done toward developing the appropriate diagnostic criteria and assessment scales in order to improve our diagnosis of depression in AD patients. The tools designed for use in the general population of older adults may not be optimal. They do not capture the unique features of depression in

¹ Alzheimer Disease (AD) in this dissertation is interchangeably written with Alzheimer's Disease, or Alzheimer's disease, depending on the names of the scales or diagnostic criteria. In all other cases the terminology follows that used in the journal of "Neurology".

dementia, as they rely on self-reporting of symptoms, which patients may not be able to optimally express due to various levels of cognitive impairment.

The work presented here sets out to contribute to the overall understanding of depression in AD, specifically in the light of assessment and diagnosis. To achieve this goal, the nosology of depression in older adults was studied, followed by a review of the associated multiple risk factors. In addition, the prevalence, and the impact that depression has on the patient, their caregivers, and society are reviewed. The presentation of depression, in terms of behavior and neuropsychological factors, was examined followed by an appraisal of the major neurobiological hypotheses regarding depression in older adults. Given that the focus of this study was depression in AD patients, important topics such as what is AD and why study it, and what is depression in AD (dAD), are described before going into the neurobiology and neuropsychology of depression in AD. I also introduce the new diagnostic criteria for depression of AD (the Provisional Diagnostic Criteria for depression of AD: PDC-dAD)² to discuss the state of the current diagnostic approaches. The neurobiology of depression is addressed for the purpose of comprehensiveness and speculation that the underlying biological underpinnings for dAD differ from Major Depressive Disorder (MDD). Finally, pharmacotherapeutic approaches and assessment scales for depression in AD are reviewed.

The background and introduction of this dissertation includes Chapter 1 and 2. The body of the dissertation includes three studies evolving around the new diagnostic criteria (i.e., PDC-dAD): a comprehensive review and a meta-analysis examining the validity-evidence for the

² Provisional Diagnostic Criteria for depression of Alzheimer's Disease (PDC-dAD) are referred to as NIMH-PDC-dAD, PDC-dAD, PDC, or dAD, or depression of AD, depending on whether the reference is the diagnostic criteria or depression specific to AD. Depression of AD, differs from depression in AD, in that the latter is associated with diagnostic criteria other than the NIMH-PDC-dAD including DSM criteria.

PDC-dAD; an empirical observational study assessing the utility of depression scales for use with the PDC-dAD; and a content validity survey of the Geriatric Depression Scale for use with the PDC-dAD, using content experts to judge the quality and representativeness of the items of the depression measure for measuring the construct of interest (the PDC-dAD). The dissertation ends with an overall appraisal of the findings and a general discussion.

In Chapter 1, depression in older adults will be examined for nosology, prevalence, risk factors, consequence, presentation, neurobiology, and assessment scales. Exploring depression in older adults (late-life depression) allows for a better understanding of depression of AD in the larger context of aging.

Chapter 2 (depression in AD) defines Alzheimer's disease and shows why we need to study AD and depression. This chapter reviews major neurobiological hypotheses evolving around depression, neuropsychology of depression in AD in terms of differential diagnosis and correlation between insight and depression, and the impact that depression of AD has on the patients and their caregivers. Subsequently, the new depression diagnostic construct, the PDC-dAD, will be introduced, and specific pharmacotherapeutic approaches for depression of AD (dAD) will be reviewed in relation to different diagnostic criteria and assessment scales. Finally, depression assessment scales will be appraised.

Chapter 3 (Study one) aims to show validity of the Provisional Diagnostic Criteria (PDC) for depression of AD (dAD). Current evidence about the PDC is scattered and hard to make sense of. Given the available meta-analytic tools, I think that the current evidence can be appraised to provide validity-evidence for the PDC. Thus, for the first time, with the use of meta-analytic techniques, current evidence (epidemiological data, psychometric, clinimetrics, clinical trials,

and external validators) is assembled to examine and to comprehensively review the validity of the PDC-dAD.

Chapter 4 (Study two) sets out to enhance assessment and recognition of depression of AD by an observational cross-sectional examination of informant and self-report-type depression scales. I hypothesize that depression screening measures developed for older adults and validated for the DSM can detect depression of Alzheimer's Disease (dAD) as defined by the 2002 NIMH-PDC-dAD; given that the PDC-dAD and DSM-MDD have overlap in terms of symptoms.

Chapter 5 (Study three) presents a content validity assessment survey, where the validity of the Geriatric Depression Scale (GDS) for use with the PDC-dAD is studied both quantitatively and descriptively. Precisely, for the first time since the inception of the GDS, with the aid of content validity techniques, and via experts' review of the assessment scale for content appropriateness and quality of the items, the GDS is put under scrutiny for use with the novel diagnostic criteria, the PDC-dAD. I hypothesize that the GDS has content validity for the PDC-dAD; however, it has to be shortened or optimized for content. Additionally, I anticipate that the content validity of the GDS-30 has implications for the use of the shorter versions of the GDS, notably the GDS-15, for screening with the PDC.

I anticipate that the current evidence supports the validity of the PDC, and highlights the PDC as the best available standard for diagnosing depression in AD; however, it may need optimization. The emerging results from Study 2 and 3 will facilitate scale selection for screening depression of AD. They will allow a better understanding of the phenomenology of depression in AD.

Chapter 1. Depression in older adults (late-life depression)

Definition of depression (nosology)

It is a misconception that depression is a normal and inevitable part of aging.^{1,2} Nonetheless, depression in older adults is highly prevalent and is associated with poor prognosis.³ Depression affects not only the individual, but also their care provider, and impacts the society at large. Depression manifests in several ways, and the diagnosis of depression is aided by multiple tools in clinical and research settings.⁴ These tools include the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria,⁵ International Classification of Disease and Related Health Problems (ICD),⁶ the Research Diagnostic Criteria (RDC),⁷ and the Provisional Diagnostic Criteria (PDC).⁸⁻¹⁰ Historically, the RDC was the original diagnostic tool utilized across both the North American and European countries for making psychiatric diagnosis and predated the DSM criteria that were developed and put to use in early 1980s. However, validity studies showed that items from the RDC (e.g., cognitive symptom, and concentration difficulty) needed to be omitted for diagnosing depression in AD and that the RDC has limitations such as low sensitivity for some symptoms including self-reproach or guilt.⁷ On the other hand, the ICD which was developed by the World Health Organization (WHO) focused mainly on clinical work and was not specific to psychiatric conditions. The DSM on the other hand was developed by the American Psychiatric Association (APA) for psychiatric purpose.¹¹ The DSM-IV compared to earlier versions of the DSM had a higher level of operationalization and were more geared towards research (evidence-based) criteria. Thus, most research has used the DSM criteria, and to a lesser degree the ICD criteria, for the diagnosis of depression. In recent years attempts have been made to minimize the differences between the DSM and ICD diagnostic criteria. Given that

the DSM criteria for major depressive disorder (MDD) were the precursor to the PDC-dAD, thus I have chosen to focus only on the DSM and PDC but not on the ICD or RDC diagnostic systems. As a result, for the purpose of my thesis, the DSM depression criteria are first enumerated here and briefly discussed, and the PDC are further discussed in subsequent chapters. Finally, the differences between these criteria are examined.

Major depression or major depressive disorder is one of several diagnostic categories described in the Diagnostic and Statistical Manual of Mental Disorders-Fourth edition-Text Revised (*DSM-IV-TR*) (see Appendix J). Clinical diagnosis of major depression requires that at least five of the nine symptoms (including either depressed mood or anhedonia) have been present nearly every day for at least two weeks and represent a change from previous functioning.⁵ The remaining symptoms include significant change in weight or in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or inappropriate guilt; diminished ability to think or concentrate, or indecisiveness; and recurrent thoughts of death or of suicide. The current literature does not provide guidelines on how to apply the DSM criteria for depression in older adults, and only suggests that practicing clinicians be alert for the presence of old age syndromes (such as arthritic pain, amnesia, and most importantly dementia) that may present as depression.

There are numerous other less severe depressive disorders cited in the literature. For example, *dysthymia* is a less severe, yet chronic form of a depressive disorder. This condition is characterized by depressed mood “that lasts for most of the day, more days than not, for at least two years”.⁵ For this diagnosis two or more of the symptoms are required, including poor appetite or overeating; insomnia or hypersomnia; low energy or fatigue; low self-esteem; poor concentration or difficulty making decisions; feelings of hopelessness.⁵ *Adjustment disorder with*

depressed mood, another less severe-type of depression than the DSM-MDD, arises in response to a specific stressor, such as placement in a long-term care facility or the death of a spouse or partner.⁵ *Depressive disorder not otherwise specified* includes depression secondary to another medical condition or to medication.⁵ Some experts also recognize *sub-syndromal depression* (also called minor depression) or use the DSM research diagnostic criteria (RDC), which are characterized by depressive symptoms like those of major depression, but with fewer symptoms and less impairment.¹² The variability in diagnostic criteria (see Chapter 3, table 2 for illustration of the use of various diagnostic and assessment approaches) and their variable utility in clinical practice complicate diagnostic and treatment approaches. For instance, the prevalence rate of depression in AD has been heterogeneously reported due to various assessment and diagnostic approaches, suggesting that harmonization in clinical practice is needed.

Prevalence

The lifetime prevalence of Major Depressive Disorder defined by the DSM (DSM-MDD) in people over the age of 60 sampled from populations in the community (rather than long-term care) from China (Beijing and Shanghai), Canada, and the United States, ranges from 2.6 to 10.6%.¹³⁻¹⁸ Depression affects older adults living in any setting, and its prevalence varies significantly, and increases by age.¹⁹ Among those in long-term care facilities, the prevalence of depressive symptomatology was estimated at anywhere from 6% to 44%.²⁰⁻²² Of great importance to the current work is the fact that depression was assessed or screened by multiple measures and approaches in these studies (see chapter 3, table 2) that may not have been the optimal approach for the particular population; the elderly. For instance, one study used the Minimum Data Set (MDS), which provides a nonspecific formal diagnostic approach.²⁰ Another

study used the corroborated diagnostic approach by resident psychiatrists using the DSM-revised 3rd edition (DSM-III-R), with the aid of a range of assessment measures including the Cornell Scale for Depression in Dementia (CSDD), the Feeling Tone Questionnaire, the Hamilton Depression Rating (HAMD, also abbreviated by HDRS) and the Structured Clinical Interview for DSM-III-R Personality Disorders Scale.²¹ In addition, there is no set criteria to define older adults, and arbitrarily some use over the age of 60 and others over 65. The variation in the assessment and diagnostic methods used in the studies above suggest that different depressive symptoms were examined and thus, these numbers may not reflect the true prevalence for depression in older adults. Importantly, the prevalence rate can only be applied to those individuals who attend clinics or participate in epidemiological studies. It is known that a large percentage of older adults with depression, 25 to 35%, are not participating in research projects (selection bias).²³ Furthermore, older people with psychiatric disorders utilize mental health services infrequently.²⁴ A low proportion of clinically depressed elderly individuals seek help and typically present to primary care practitioners first.²⁵ Evidence shows that primary care physician correctly diagnose only a minority of depressed elderly patients and consequently few receive treatment for their illness.²⁵ In addition, up to 75% of older adults who die by suicide visited their primary care physician within a month of their suicide,²⁶ suggesting that primary care physician tend to miss these cases. In fact, not all elderly with depression are screened for depression, which decreases the likelihood of finding depression.²⁷ Also, only smaller proportions of elderly patients are referred for psychiatric care.²⁵ Moreover, physicians caring for the elderly often misunderstand depression and depressive disorders given that they are confounded by multiple factors,²⁸ such as concomitant medical illness and normal aging.²⁹ Depression often co-occurs with other serious illnesses and elderly people may be less willing to

talk about feelings of sadness and hopelessness.²⁷ Moreover, the presence of underlying AD or other primary dementia with similar symptoms can directly affect accurate diagnostic assessment of depression.³⁰ For example, a patient with significant dysphasia may have a limited ability to report on mood state. Additionally, patients' clinical history and depressive symptoms report may be relatively unreliable because of memory deficits and lack of insight due to concurrent dementia.³¹ Thus experts recognize that depression and depressive symptoms in older adults often go unrecognized and untreated, and that the true prevalence is masked by assessment methods and selection bias.³² The selection bias may be unavoidable, given that symptoms of depression are often confounded by other psychiatric and neurological conditions, such as apathy, which impacts the functionality of the individual, and their level of interest. Thus, one may suggest that those individuals participating in research projects are in fact different from those that do not, speculating that this difference perhaps is due to underlying physiological differences in terms of depression. In other words, those participating in the studies are more functional or, if diagnosed with moderate AD, they are at the milder stages of the moderate AD severity spectrum. This is a moderating factor affecting the prevalence of depression, suggesting that the actual prevalence may in fact be higher than what is estimated. These facts highlight the need for better recognition, and assessment harmonization of depression in older adults with no dementia, a significant and important phenomenon.

Risk factors for depression

Multiple risk factors are associated with depression in older adults.³³ These could be classified into biological and psychological dynamics. From the biological perspective, gender and ethnicity are highlighted as genetic markers. Depression is more prevalent in older women than

older men; however, it is noted that, as the age increases, the gender gap narrows.³⁴ Evidence from studies examining the influence of race and ethnicity on the prevalence of depression in older adults highlight that depressive symptoms are more frequent in Hispanic older women.³⁵ For example, by using the Centre for Epidemiological Studies Depression Scale (CES-D), the DSM-MDD validated screening measure for older adults,^{36,37} one study of health and aging examined the prevalence of depression in 1,151 community dwelling, Hispanic and non-Hispanic White participants in the San Luis Valley (Colorado), United States. This showed a higher prevalence of depression in Hispanic (n=628) than non-Hispanic (n=523) older adults even after adjustment for multiple socio-demographic and health risk factors (Hispanic: 11.8 to 15.9%; non-Hispanic: 8.2 to 10.4%, depending on age range from 60 years to over 80).³⁵ It should be noted that the focus of the current dissertation is not on gender or ethno-racial differences; however, one must note that the western-Canadian population is different from the aforementioned study, in that our population holds diverse ethnic groups.

In order to differentiate the biological versus the psychological risk factors, development of depression is considered from a lifespan perspective. For example, if depression in old age is the first depressive episode of a lifetime, it is suggested and speculated that it be associated with psychological and biological changes³⁸ (such as medial temporal lobe atrophy) or environmental interaction³⁹ that an elderly individual experiences. On the other hand, if the individual sustained the first episode when they were younger, during early adult life, depression is associated with familial or genetic risk factors.^{40,41}

Other biological or psychological risk factors include chronic medical conditions (e.g., hypertension), poly-pharmacy, multiple losses (e.g., driving privileges, family or friends, autonomy, home, social interaction), functional decline (physical, cognitive, or both), personal or

family history of depression, social isolation, substance abuse or dependence, and neurological conditions (e.g., dementia, stroke). For example, a meta-analytic study showed that risk factors for depression in community-dwelling older adults were bereavement, sleep disturbance, disability, prior depression, and female gender.⁴² It is notable that these factors may not be the only ones and that other conditions may play a significant role. For instance, one study showed that 63% of visually impaired older adults reported depressive symptoms, indicating a strong association between visual impairment and depression.⁴³ As the evidence shows, sensory decline in older adults both directly and indirectly affects cognition and daily functioning, and importantly mimics or confounds depression and depressive symptoms.⁴⁴ In this vicious cycle, the state of sensory decline plays a significant role that needs to be taken into consideration in the assessment of depression. However, here these risk factors are only enumerated for the purpose of comprehensiveness of the present work and to show that some but not all items are present in most diagnostic criteria, screening and assessment scales for depression (e.g., sleep disturbance, social isolation). In fact, screening measures such as the GDS takes into account some of the confounding somatic symptoms.⁴⁵

It is often difficult to determine whether presenting symptoms are caused by depression or are symptoms of other psychological or physiological problems. Many illnesses that are common in older adults are either associated directly or indirectly with depressive symptoms, including dementing illnesses.⁴⁶⁻⁴⁹ For instance, multiple studies have shown that depression was correlated with a cascade of events such as reduced physical activity leading to cardiovascular disease.^{50,51} Furthermore, the bidirectional relationship between depression and comorbidities leads to increased complications, such that worsening in one condition often leads to worsening of another,¹ and resulting in diagnostic complication. For example, depression in older adults has

been shown to have a bidirectional relationship to cognitive functioning, such that it was correlated with lower cognitive reserve, or exhaustion of the intact cognitive abilities.^{52,53} Moreover, general cognitive impairment may induce or mimic depressive symptoms. As the individual ages and sustains cognitive changes accompanying normal aging, and experiences biopsychosocial losses (e.g., change in functional ability and loss of family members or friends) depressive symptoms may emerge. This fact also influences the understanding of the pathophysiology of depression, particularly with individuals with multiple diseases and disorders. For example, in elderly individuals with sensory decline and cognitive impairment leading to dementia, understanding of the co-occurring depression may not be easy. As a result of these co-occurring factors, the road to the etiology of depression in terms of psychological, social, and biological factors is unclear, highlighting the urgency to study depression in older adults.

Depression in older adults has been suggested to be a non-biological marker of late life dementia,^{54,55} or a prodromal manifestation of AD.⁵⁶ It is important to re-emphasize that the current evidence on the topic is based on heterogeneous sets of assessment scales and diagnostic approaches to depression. Some of the evidence refers to depression or depressive symptoms that are heterogeneous in presentation that can be confounded by other conditions. Resolving this dilemma – depression being a risk factor for dementia versus a prodromal presentation – is beyond the scope of this dissertation and only a few facts on the accepted knowledge about these ideas are highlighted. For instance, depression presenting as a risk factor for AD was observed in a retrospective study of 243 AD patients.⁵⁵ In this study, AD patients, but not healthy controls, had a higher rate of premorbid depression. In this study, a geriatric psychiatrist with access to informant knowledge of the patients' history, and depression symptoms measured using the

CSDD cutoff scores of 7 for DSM-III-R, diagnosed depression. Others however, based on the study of epidemiological data, believe that late-life depression, mild cognitive impairment (MCI), and dementia are part of a continuum. Late life depression without signs of dementia is an alternative clinical presentation of dementia.⁵⁷ This concept is critical and the new McKhann et al. criteria for AD/dementia (2011),⁵⁸ which include change in behavior, address this possibility. According to the McKhann criteria, changes in personality, behavior, or ‘comportment’ include uncharacteristic mood fluctuation such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsivity or obsession, and socially unacceptable behavior.

In sum, in the elderly, depression maybe the manifestation of single or multiple factors (e.g., sensory loss, global cognitive deterioration, physiological impairment), which render the understanding, assessment and diagnosis of depression difficult. These factors should inform the development of assessment scales or diagnostic criteria that are appropriate for depression in the elderly.

Impact of depression

Depression not only impacts the patients, but also their families and society. Depression in older adults hinders compliance with medical treatment, decreases physical strength, increases disability, and influences the quality of life (QOL). Also, it is a known risk factor for suicide (a commonly perceived solution to intolerable psychological and physical suffering), and eventually, mortality due to accelerated aging or early placement in nursing homes.

Depressed older adults residing in nursing homes have an increased likelihood of mortality. In fact, one study showed that the likelihood is about 60% after diagnosis for major depression.^{59,60}

This study consisted of 77.3% female subjects, and depression was diagnosed according to the DSM-MDD-third edition, and corroborated with four independent sources, including psychiatric evaluation, nursing home staff and family informant, and medical records. The majority of the sample from this study was of the age 75 to 84 (45.6%), and 34.6% of their sample consisted of elderly individuals of the age 85 and older, which is consistent with the current knowledge that with age the prevalence of depression increases.¹⁹

In 2007, the National Institute of Mental Health (NIMH) reported that successful attempted suicide in older adults is higher than in the general population. The study showed that 14 deaths per 100,000 are seen in people aged 65 and older, in contrast to 11 deaths per 100,000 in the general population.⁶¹ Moreover, a 2004 study using only 8 items of the CES-D (not the complete 20 items) found that depressive symptoms in older adults were independently associated with higher levels of informal care giving, even after controlling for persisting comorbidities.⁶² The authors of this study also concluded that the additional care giving hours associated with depression represented “a significant time commitment for family members and, therefore, a significant societal economic burden” (P. 857).⁶² It is noteworthy that studies also found that depression (minor and major depression as assessed by the DSM-IV and CES-D) can alter self-perceptions and leads to over-reporting of functional disability.⁶³ For example, one cross-sectional study compared the health records of 6257 outpatients with diagnosis of depression made by the primary care provider to 6257 primary care patients without depression, and showed that patients with depression accrued higher annual health care costs for every examined category of care.⁶⁴ This study did not provide specifics as to the diagnostic approach, given that medical records were used to gather the data, which complicates interpretation. Considering that older adults have a disproportional burden from physical health concerns, the cost of concurrent

depression in the elderly individual substantially increases.^{65,66} These societal burdens are an urgent call for research on depression in older individuals, in terms of screening, assessment and diagnosis, with an aim to enhance our understanding of this phenomenon and eventually minimize future burdens.

Presentation

Depression in older adults can present in numerous ways, and many symptoms overlap with the manifestation of physical illnesses common in this population (e.g., arthritic pain), complicating recognition.⁶⁷ Physical signs and symptoms of depression may include weight change, sleep impairment, psychomotor changes including slowed movement, and vague complaints of pain. Individuals may experience memory and executive functioning problems such as loss of concentration or difficulty making sound decisions. They may become more demanding or apathetic. It is also usual for an older individual to deny feelings of sadness while exhibiting other signs of depression. It is possible that the current diagnostic approaches for depression in older adults without dementia are not suitable given the heterogeneous presentation of symptoms.⁶⁸ In fact, experts highlighted several depression presentations in older adults. For example, some postulated the presence of “vascular depression”,⁶⁹ “depression without sadness”,⁷⁰ and “depression-executive dysfunction syndrome of late life”.⁷¹⁻⁷³ In short, depression in older adults differs in terms of symptomatic presentation compared to other age groups, with or without cognitive impairment; therefore, depression in older adults may need its own diagnostic criteria. For example, similar to what is proposed for AD, the cognitive component in DSM-MDD may need to be removed/replaced by another item, given that cognitive impairment is a part of normal aging.

Depression in older adults differs from that in younger adults, specifically in terms of symptoms presentation.⁶⁸ For instance, suicidal ideation and behavior in older adults differs in several respects from that of younger adults. Older adults with depression tend to be less verbal and more ideational about suicide.³³ When it comes to suicide, they talk about the idea of death, but they do not necessarily act on it, and when they act on it, they do not talk about it beforehand. Additionally, the prevention of a suicide attempt is even more difficult in older adults given that suicidal older adults often go undetected in a visit with a physician before the act. In fact, current evidence shows that older adults make a visit to a physician shortly before attempting suicide.⁷⁴ Current evidence does not show clear reasons for this phenomenon.

Neurobiology of depression in older adults

The neurobiological factors underlying depression in older adults are complex and, although not completely understood, comprise anatomical and molecular neurological changes in the central nervous system (CNS). From the molecular view, the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (*DSM-IV-TR*), states that the pathophysiology of depression revolves around "dysregulation of a number of neurotransmitter systems, including monoamines such as the serotonin (5-HT), norepinephrine (NE), dopamine (DA), acetylcholine (ACh), and gamma-aminobutyric acid (GABA) systems".⁵ It is hypothesized that the imbalance in the monoamines may occur "either through excessive pre-synaptic up-take or through stress-related down-regulation of post-synaptic receptors."⁷⁵⁻⁷⁷ Of essence, these dysregulations are based on the studies of major depression or depressive mood as diagnosed or classified by DSM-IV that is specific to idiopathic depression seen in general population. This is an important factor that will be

explained further in later chapters. The original monoamine hypothesis of depression goes back 50 years,⁷⁸ when individuals with high blood pressure were given reserpine and showed severe depression. Although not accepted by all as depressogenic,⁷⁹ some suggests that Reserpine deplete monoamines including DA, NE, and 5-HT.⁸⁰ This finding was the precursor to the monoamine deficit hypothesis of depression, suggesting that depressed individuals generally might have lower levels of these neurotransmitters. This is the reason for the emergence of compounds such as monoamine-oxidase inhibitors and Selective Serotonin- Reuptake Inhibitors (SSRIs).

The major source of 5-HT in the brain is the raphe nuclei in the brainstem. Raphe axons project to many regions throughout the brains (e.g., hippocampus, septum, amygdala, frontal and limbic cortex), and modulate other neurotransmitter systems that are important for an understanding of the etiology of clinical depression. The main role of serotonin is to regulate the behavioral inhibitory system controlling aggression, anxiety, circadian rhythms, food intake, impulsivity, mood, and sleep.⁸¹ Importantly, it is noteworthy that imbalances in these multiple functions are recognized as symptoms of major depression by DSM criteria. To this end, SSRI agents with lower side effects are prescribed for alleviation of depressive symptoms. It is noteworthy that, SSRIs have distinct pharmacological qualities; in comparison to tricyclic antidepressants, they all have selective and potent inhibitory function on 5-HT reuptake. The SSRIs are thought to act at both the presynaptic axon terminal and somatodendritic end of the 5-HT neuron (near the soma) at the midbrain raphe to increase 5-HT levels where it is hypothesized to be deficient.⁸²

Current evidence also shows a relationship between reduced DA transmission and major depression by DSM criteria.⁸³ The role of DA in depression is supported by regional specificity

of multiple projections of the dopaminergic neurons from the ventral tegmental area, located close to the midline on the floor of the midbrain (mesencephalon), to cortical and subcortical regions such as the prefrontal cortex, striatum, and anterior cingulate. Each projected area is involved in multiple functions and behaviors; for example, the prefrontal cortex is related to decision-making and attentional ability, while the striatum is related to planning and modulation of movement, and working memory. Evidence shows that the abnormal functioning of these projections leads to various symptoms of depression, such as the lack of concentration or the ability to make sound decisions, or slowed reaction time.⁸⁴ It is essential to note that these symptoms are primarily cognitive in nature rather than affective, and their presence may not necessarily suggest the presence of depression. For example, most Parkinson's patients without diagnosis of depression present with these symptoms.⁸⁵ Moreover, these symptoms may not be present on a daily basis over the period of two weeks, the temporal hallmark of the DSM diagnostic criteria for major depression. Similarly, these symptoms may present with AD or other neurodegenerative conditions. These facts highlight the need for a specific diagnostic framework that removes cognitive considerations from the assessment of depression in neurodegenerative illnesses, such as in AD (discussed in more detail in Chapter 2). On the other hand, because the dopaminergic system is widely spread across brain regions, no study has shown whether dopaminergic stimulation alone can alleviate depressive symptoms.⁸⁶ Nevertheless, direct and indirect evidence exists to support the involvement of the multiple dopaminergic systems in major depressive disorder as per DSM. Furthermore, an elevated level of dopamine metabolite in the cerebrospinal fluid (CSF) of depressed AD patients in comparison to the non-depressed as diagnosed by the GDS-15 has been observed.⁸⁷ The presence of DA metabolite in the CSF may suggest the lack of global DA up-regulation.

Another line of evidence supporting the relationship between depression and the neurotransmitter DA is based on the role of antidepressant efficacy of compounds whose natural effects include increasing DA.⁸⁸ Although this evidence lends a strong support for the relationship between depression and DA, there is no direct support for the causal role of DA.

The role of Ach in depression and mood disorder in general has been extensively studied.⁸⁹ A significant body of literature suggests that the cholinergic nervous system, which emanates primarily from the entorhinal cortex (EC), alone or in combination with other neurotransmitters (e.g., 5-HT),⁹⁰ may have a key role in the regulation of affect,⁹¹ and consequently in the etiology of depression. These regions are affected by the normal aging process and AD pathology and thus differentiating the impact of depression from AD pathology on these regions is complicated. Thus, to date, no study has explicitly stated that the function of these neurotransmitters is specific to depression in AD.

At the structural level, multiple risk factors are highlighted. As the individual ages and neurodegenerative processes become more pronounced, neuronal loss⁹² with subsequent neuronal network disruption, atrophy and change in the shape of the brain as a result of both grey and white matter alterations,⁹³ and changes in the cerebrovascular function⁹⁴ are expected. However, there are some risk factors, in isolation or in combination, that are underscored to be possible factors for increasing the risk of developing depression in older adults. For instance, studies have shown that medial temporal lobe atrophy, particularly at the level of the hippocampus, is correlated with depression. These studies classified individuals as depressed when a CES-D score of 16 or higher was present or a diagnosis of major depression by DSM criteria was made in older individuals.⁹⁵⁻⁹⁷ However, the samples consisted of a heterogeneous group of patients with differing levels of depressive symptoms and diagnosis. Given the stress

model of depression (discussed below), where it is postulated that the hippocampus is more vulnerable to long-term stress, substantial changes in its structure have been considered as evidence to confirm its involvement in depression when individual symptoms are present.^{96,98-100} Nonetheless, whether changes in the hippocampal structure is due to cognitive change or stress is not clear or confirmed.

The stress hypothesis model and the involvement of the hypothalamic-adrenal system (HPA axis, also known as the limbic-hypothalamic-pituitary-adrenal axis) has been another avenue of research for clarifying the neurobiological substrate of depression.¹⁰¹ It is postulated by the stress hypothesis model that stress activates the HPA axis through different pathways, affecting monoamine neurotransmitters including 5-HT, DA, and NE, essential in regulation of the HPA axis. However, before we understand how these neurotransmitters are altered or have a significant role in the HPA axis, it is important to know the normal function of the HPA axis. In short, the HPA axis interacts among glands, hormones, and parts of the midbrain that mediate functional adaptation in reactions to environmental stimulus, i.e., stress. By modulating stress hormones such as cortisol – which helps to maintain bodily homeostasis, including mood and emotions, among other bodily functions – the HPA axis in a normal state deflects stressors. However, chronic stress alters the normal HPA axis functioning. For example, a body of literature convincingly shows that chronic stressful events occurring in earlier life despite normal functioning predate depression in late adulthood.¹⁰² Of note, it appears as if the individual has never recovered from the impact of earlier depression, which shows how detrimental is the impact of this stressor on an individual. Additionally, evidence from antidepressant clinical trials have shown that over-exertion of the HPA axis has been present in a majority of individuals experiencing depression, and the over-exertion is attenuation via treatment.¹⁰³ Moreover, review

papers have highlighted the neuronal circuits of HPA dysfunction relating to depression symptoms, including hypercortisolemia and resistance to feedback inhibition, and adrenal and pituitary hypertrophy in stressful events,¹⁰⁴ and hypercortisolemia normalization after successful antidepressant treatment.¹⁰⁵ These are some of the underlying reasons for believing why multiple systems are involved in the etiology of MDD,⁸⁸ and particularly with regards to the involvement of the HPA axis. However, there is no clear relationship between depressive symptoms as per DSM criteria, and attenuation and management of the HPA exertion. This shortcoming emanates from several factors that involve both clinical and animal model studies. For instance, in clinical trials, patients with depression of mixed severity are included due to sampling concerns; and depression diagnosis involves inclusion of a range of heterogeneous sets of symptoms, which make the comparison, at the individual level, difficult. These are generally neurobiological reasons attempting to explain depression that follows DSM-MDD criteria that is not specific to depression in AD, which is not well understood in terms of clinical symptoms, diagnosis, and neurobiology. Nevertheless, these are the closest approach to understanding depression that is not based on a systems sustaining neurodegeneration.

The comprehensive understanding of the neurobiology of depression remains elusive to this date because A) depressive syndromes are heterogeneous and their aetiologies diverse, and B) symptoms such as guilt and suicidality are impossible to reproduce in animal models.¹⁰⁶ Nonetheless, there are multiple hypotheses to explain this phenomenon based on clinical studies of general populations, older adults with and without cognitive impairment of various degrees, and pre-clinical animal models. These hypotheses about the neurobiology of depression in aging are complex, controversial, and beyond the scope of the present work to be discussed in detail. Hence, only the ones with the most relevance to AD will be discussed in detail in this work.

In brief, the neurobiology leading to the etiology of depression shows signs of mixed results, whose interpretations remains complex. There is extensive literature to show morphological and neurochemical differences between depressed and non-depressed older adults; however, very few, if any, have clearly shown the link between the heterogeneous range of symptoms and impairment of a specific brain region.

Depression assessment scales

There are a plethora of depression scales in existence,^{107,108} and their optimal utility is dependent on the goal of the user.¹⁰⁹ However, only a few scales have been specifically designed for older adults (e.g., the GDSs,^{110,107} the Hubley Depression rating Scale for Older Adults [HDS-OA],¹¹¹ the Cambridge Examination of Mental Disorders of the Elderly [CAMDEX],¹¹² the CSDD,¹¹³ the Dementia Mood Assessment Scale (DMAS),¹¹⁴ and the Canberra Interview for the Elderly (CIE),¹¹⁵ among others).¹¹⁶

Generally, the scales can be divided into multiple categories based on how they are formulated, how they retrieve responses, or who rates the patient. With regards to formulation, some of the scales are DSM-based while others are not; with regards to response format, there are scales that have a Likert-like scale response format (e.g., the CSDD), while others use the dichotomized (Yes/No) type format [e.g., the GDSs (GDS-30, 15, or 10 items) and HDS-OA]. With regards to who rates the symptoms, there are scales designed to capture both the patient and the informant view of the symptoms (e.g., the CAMDEX¹¹² or CSDD) versus others that capture only patient or informant collateral response at one time (e.g., GDSs for patients, or GDSIF-30 for informant collateral). Additionally, other factors also serve in classifying scales, such as the time that it takes to administer them or how they are administered. For example, some are short

and can be administered within minutes (e.g., GDSs), whereas others are relatively time-consuming (e.g., the CSDD); as well, some are interview-based (e.g., the CSDD) while others are self-administered or administrator-read (e.g., GDS for patient or for informant). Some of these scales are psychometrically validated against the DSM or other diagnostic criteria, or cross-examined with other depression scales (e.g., the GDS vs. the Beck Depression Inventory, BDI), and with differing elderly samples. For example, the GDS was developed based upon a sample of elderly individuals, inpatient/outpatient geriatric population with and without depression⁴⁵ and potentially with some level of cognitive impairment.

These variations in the scales raise multiple concerns with regards to their utility in the context of the current diagnostic frameworks. First, few of the DSM-based scales are specifically designed to screen for depression in older adults with cognitive impairment, where cognitive deficits limit an individual's ability to relate their symptoms. Second, there is the absence of a well-validated easy-to-use screening measure for use with PDC-dAD, in the form of self-report with a comparable informant-based version. Third, what is indispensable for research (to gather all possible information about each patient) often exceeds what is desirable for quality clinical examination.¹¹⁷ In other words, the balance between time, cost and efficacy to treat the patient is indispensable for clinical work, rather than screening for all symptoms for each patient. Fourth, some of the scales de-emphasize vegetative symptoms (e.g., eating or sleep impairment), or somatic symptoms (e.g., the GDS de-emphasizes somatic symptoms). Finally, some scales are more suitable for detection of major depression than of dysthymia or of a history of depressive disorders,¹¹⁸ while others require considerable clinical skill and sound decision-making ability to be reliably administered (e.g., the HAM-D). This heterogeneity in the range of available depression scales complicates understanding of depression in older adults.

On the other hand, there are some psychometric and clinical questions emanating from the large list of assessment scales. For example, how well do they discriminate depression in older adults? What have been some of the problems? Are they roughly equivalent? Which appear better, and which are better accepted by people?

The value of the scales varies as a function of the goal that they intend to accomplish, and the cost to benefit ratio regarding their practicality. The first tends to depend heavily on the psychometric properties of a measure. For example, for measuring depressive symptom severity, the scales' reliability over time is crucial; to examine for suicidal ideation or possible future suicidal attempt, the scales' high sensitivity is of greater value so that we do not miss the possible cases. However, other psychometric factors play a significant role too, such as the length of the scale, or how the scale is administered. For example, for patients with a low level of cognitive impairment, the self-report may simply suffice; however, with individuals with more cognitive impairment, a scale with lower cognitive complexity (e.g., in the number of individual items, readability, response format) and an administrator-read approach would be a superior method. These factors play a considerable function in terms of scale selection and use.¹⁰⁹

Length of the scale (brief vs. large)

Clearly, there are differences between the two lengths of the scales, and that is the time taken to complete the questionnaire or administer it to the patients. The brief scales are set to capture a significant amount of information in a limited time, notably via a yes or no (dichotomized) type response format. They usually take a few minutes: 5 to 10, sometimes shorter. For instance, the 10-item Patient Health Questionnaire (PHQ-9), which has all the symptom items of the DSM-MDD that is not specifically designed for older adults, requires roughly 5 minutes, and for its shorter version, the PHQ-2, 2 minutes are maximally desirable to collect the needed information

regarding the depressive mood of the individual in the clinical setting. The primary care professionals for screening of depression symptoms usually use these shorter scales; and they are seldom used for research purposes. On the contrary, the larger scales, such as the CSDD, are intended to capture greater amounts of information relative to the shorter scales and take about 20 to 45 minutes to be administered. These longer scales may incorporate informant collateral information, and tend to provide more information leading to the assessment of the severity of depression as opposed to only an assessment of the state of depression (present or absent).

Response format (dichotomized vs. Likert-like format)

Dichotomized response formats are easier to administer to patients with cognitive impairment; however, they have limitations, in that it is harder to assess severity or reach to the underlying cause of depression given that not enough information or nuance has been examined.

Nonetheless, there are scales that are short and have a dichotomized response format that allow classification of the depression severity by the obtained scores. For example, although not specific to the geriatric population, the PHQ-9 uses cutoff scores that classify depression from non-existent to mild to severe in magnitude. A similar approach is available with scales using the Likert-type approach, such as with CSDD; however, these are more cognitively taxing or, at times, time consuming.

Discriminating depression in older adults

Although there is no consensus as to which scale is better for which purpose, generally, the assessment/screening scales have shown good psychometric properties, such that their sensitivity and specificity were ranked good to high. It is noteworthy that the same psychometric level may not apply to a different setting or different population. Given the scope of the current work, it is impossible to examine here the level of discrimination of each depression measure available to

date. However, for the most popular, given their shortness or how they were developed, the GDS and BDI can be named as examples. Specifically, the GDS-30, a short scale with a dichotomized response format, has been shown to have an acceptable sensitivity (82.2%) and specificity (81.3%) with cognitively impaired inpatients diagnosed for major depression by the DSM-IV criteria by a psychiatrist.¹¹⁹ Similar results have been found with the BDI, a relatively more complex scale with a Likert-like response format, with inpatient¹¹⁹ and outpatient older adults.¹²⁰ In this last study, a psychiatrist using the DSM-III-R criteria for major depression diagnosed the subjects. Of note, these two scales not only differ in terms of response format and number of items, but also in terms of cognitive complexity required to complete them and the underlying construct. The BDI takes into account the required 2 weeks interval as proposed by DSM-MDD versus the GDS that does not. For research purposes, several other instruments have been developed based on the DSM criteria that equally differentiate the depressed from the non-depressed in the general older population; for instance, one can refer to the CES-D that has acceptable psychometric properties to be used in epidemiological large scale studies, given its shortness and cost-effectiveness.

Additionally, only limited data exist to show the difference or the cross-examination of the scales specifically developed for use with the elderly versus scales that were developed for the general population but put to use with the elderly. Although inconsistent in terms of outcome and assessment scale used, most of these data emerged from the study of elderly persons suffering from depression with other co-morbid conditions. For example, one study evaluated elderly (age 65 and over) undergoing hemodialysis to compare the GDS-15 to the BDI and showed that the GDS-15 has higher accuracy than the BDI (area under the curve: 0.808 and 0.729, respectively).¹²¹ In this study, patients were diagnosed for depression based on psychiatric

clinical interview. Similarly, another study examined the GDS-30 versus the BDI with elderly individuals (aged 60 to 78) suffering from generalized anxiety disorder and depression, and found that the BDI had higher overall discriminant classification score than the GDS-30, 79.6% versus 72.2%.¹²² No accuracy estimate was reported in this study.

By the same token, another study of older adults (age 65 and over) examined the GDS-15 versus the Patient Health Questionnaire (PHQ-9) and found that for major depression, the PHQ had higher accuracy than the GDS-15 (area under the curve: 0.87 versus 0.81). Equally, for major and minor depression combined, the PHQ outperformed the GDS-15 (area under the curve: 0.85 and 0.71). Of essence, the larger AUC value for the PHQ in contrast to GDS can be explained by the fact that the PHQ-9 replicates DSM-MDD criteria but not the GDS. In this study, patients were diagnosed with depression via a DSM-based Structured Clinical Interview for DSM Disorders (SCID).¹²³ In contrast to the above-mentioned GDS studies, only one study cross-examined the HDS-OA versus the BDI in adults (age 43 to 84), and showed that the HDS-OA had a very high accuracy (area under the curve: 0.98).¹¹¹ Although no result was reported for the BDI, it is hard to suggest that the BDI outperformed the HDS-OA given the high accuracy estimate reported. In sum, in terms of depression assessment scales, there are many scales available to both clinicians and researchers with a variety of psychometric properties that would allow assessing their utility for a particular aim or population of interest; however, there is no consensus generally as to which scale is better or more accepted. Given the variation in the accuracy estimates and psychometric properties of the scales, it is hard to say whether scales purposely developed for older adults are outperforming the scales developed for general population but also used with the elderly.

When it comes to screening of late-life depression, a self-report scale that is short and reliable, easily administered, with high clinical accuracy, and valid psychometric properties is desired. Additionally, given that older adults generally experience somatic physiological changes, scales that do not evaluate somatic symptoms are preferred. The most conceptually solid scale for use with older adults was reported to be the GDS-30.¹²⁴ It is arguable that other scales, such as the HDS-OA, that were developed to overcome the shortcomings of the GDS can also be recommended.

Chapter 2. Depression in AD

Why study Alzheimer's disease?

Alzheimer's disease (AD), the most common neurodegenerative disorder in the elderly, with a global prevalence estimated at 26.6 million,¹²⁵ is on the rise,¹²⁶ and has no cure as of yet.¹²⁷ The Canadian report *Rising Tide* shows that AD is the leading form of dementia, accounting for 63% of all dementias.¹²⁸ Currently, an estimated 300,000 Canadians over the age of 65 have AD. The estimated cost associated with AD is \$15 billion due to direct (e.g., patient management) and indirect (e.g., working time lost to care for proxy with AD) expenses. Given the estimated increase in AD prevalence, and the demand for long-term care, the projected economic burden for the next 30 years in Canada is \$153 billion.¹²⁸ This is a 10-fold increase in the cost of care, and is one of the primary reasons for studying treatable aspects of AD. It is noteworthy that the key driver of the cost associated with AD care is the severity of the sufferers' functional disability, which in turn increases the burden on the caregiver in the form of depression, anxiety, medical illness, poorer general health, and mortality.¹²⁹ If, in addition to these numbers, the cost associated with affective disorders is considered,⁹ it seems likely that depression and other neuropsychiatric symptoms are factors escalating the cost of care in AD. Therefore, the ability to stabilize the disease state is potentially an avenue to reduce the cost to society at large.¹³⁰

Why study depression in AD?

Current evidence shows that depression in AD may be under-diagnosed and under-treated when DSM-Major Depressive Disorder (MDD) criteria are applied.^{131,132} In fact, depression recognition is relatively low in nursing home resident, with only 37%-45% of cases diagnosed by psychiatrists recognized as depressed by staff.²¹ The reported prevalence of depression in AD has

been incredibly variable ranging from 0 to 86% as per DSM major depressive episode criteria.¹³³ (See Appendix J for DSM depression criteria) This variability highlights the lack of consensus in the field where currently no standardized methods exist to diagnose depression in AD, and different diagnostic frameworks are applied (e.g., DSM, PDC-dAD).¹³⁴ Beyond the diagnostic variation, there is also substantial variability in the scales used to assess depression, the symptoms that are evaluated and the validity of the scales for the identification of dAD. The wide range of prevalence estimates impacts resource allocation for recognition and management of depression in AD. There is a clear need for a greater homogeneity in assessment methods and diagnostic approaches.

Depression is an important complication/comorbidity observed along the entirety of the AD severity spectrum.^{135,136} The high prevalence of depression in older adults with cognitive dysfunction, and evidence pointing to depression being either a risk factor for dementia or being a prodromal stage of dementia stimulate a greater need for understanding and evaluating depression in AD. In essence, depression affects the progress of cognitive decline in both older adults with and without Alzheimer's disease, and affects cognition globally, such that speeded cognitive processing diminishes once depression is present.¹³⁷ Depression in AD and in older adults is considered as under-diagnosed and under-treated, because, among other reasons, symptoms of depression are confounded by symptoms emerging as a result of physiological changes. The presence of multiple conditions additionally complicates diagnosis and thus non-medical specialist practitioners with limited knowledge of depression in the geriatric population tend to miss or misdiagnose them. On a different note, both older adults and AD patients with depression tend to show similar symptoms such as social isolation and irritability.¹³⁸ These are some of the reasons for why understanding of depression in AD requires special attention.

Impact of depression on patient and caregiver

In AD, depression exacerbates symptoms,¹³⁹ is associated with greater severity of neurocognitive impairment,¹⁴⁰ and acts as a catalyst of cognitive decline and earlier placement to nursing homes.^{131,139,141,142} For example, in a cross-sectional study design, one group examined the cognitive difference between 105 depressed and non-depressed mild cognitive impairment (MCI) individuals (aged 40 to 94), recruited from the Facing Rural Obstacles to Healthcare Now Through Intervention, Education & Research (FRONTIER) project. In this study, GDS-30 was used to assess depression and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess cognition. Patients with depression and MCI performed substantially worse on several cognitive measures, notably on the immediate memory ($t = 3.4$, $p < 0.01$) and delayed memory ($t = 2.8$, $p < 0.01$) components of the cognitive scale.¹³⁹ The depressed group was different from the non-depressed by a magnitude of 2.9 (Cohen's d) on the GDS, which is a large effect-size. Of note, the above cognitive function differences have several times been highlighted by many.^{131,143} In the same vein, another longitudinal study examined the progression of disease in 29 patients with dementia and depression versus 26 demented individuals with a comparable cognitive level of impairment at baseline, over 12 months. This study found that demented individuals with comorbid depression required a higher level of care than those demented but not depressed.¹⁴⁴

The accrued evidence shows that depression hinders anti-dementia treatment and complicates differential diagnosis. Furthermore, depression increases morbidity and mortality.¹⁴⁵ For example, the mortality risk of depression in dementia, particularly due to suicide, is reported to be twice as high as those demented without comorbid psychiatric condition.¹⁴⁶ A post-mortem

study has shown that older people who committed suicide had higher AD pathology, including neurofibrillary tangles in their brain not yet identified prior to their demise.¹⁴⁷

Depression in AD reduces the quality of life of the affected individuals and their caregivers.¹⁴³ Depression in the affected individual likely increases the burden of the caregivers and, possibly as a result, caregivers have been shown to over-report depressive symptoms of the individual with dementia.¹⁴⁸ This evidence highlights the need for research on depression in AD.

A new construct: depression of Alzheimer's disease (dAD)

A panel of experts in 2002 suggested that dAD is a distinct disorder with features and a course different from DSM-MDD, in that signs and symptoms of dAD are less severe.¹⁰ In addition, they suggested that dAD differs from MDD in terms of prevalence, history of depression and family history, severity/frequency of symptoms, lower number of suicidality, duration of episode, outcome, and therapeutic response. Gender difference in dAD is subtle or at all not existent and psychosocial factors may be less important.^{8,10} The dAD core characteristics include dysphoria and loss of interests.^{8,9} Additionally, the PDC criteria were developed to better differentiate symptoms of depression in AD from dementia symptoms. These differences are reviewed in detail and highlighted in the next chapter discussing the provisional diagnostic criteria specific to depression in Alzheimer's disease (PDC-dAD). Briefly, the PDC have been specifically formulated to facilitate research and better recognition of clinical features of dAD.¹⁴⁹ The use of the PDC has only recently gained momentum and it has been used in large-scale international clinical trials examining SSRI treatment effects.^{150,151} Moreover, since their inception, the PDC have been used in multiple observational studies for comparison with other diagnostic criteria or screening measures to examine its validity.^{134,152-154,155}

Neurobiology of depression in AD

The neurobiology of depression in AD is equally as complex as the neurobiology of depression in older adults. Here only the main established hypotheses centered on the etiology of depression in AD are discussed. For example, recent studies, generally using postmortem investigations, neuroimaging, or psychopharmacological research, have focused on the roles played by dopamine (DA), inflammatory cytokines (e.g., Interleukin 6, or 1),^{38,156,157} genetic markers (e.g., presenilin-1 mutation, but not ApoE),^{158,159} cardio and cerebrovascular abnormalities,⁹³ and neuroanatomical correlates in dAD.^{160,161}

As previously mentioned, the acetylcholine (ACh) hypothesis (commonly referred to as the cholinergic hypothesis) is one leading hypothesis for the etiology of depression in AD. It has been hypothesized that a reduced synthesis of ACh resulting from AD pathology in the entorhinal cortex (EC), the major source of ACh, may be a factor in dAD.¹⁶² The EC is the main interface between the hippocampus and neocortex and plays an important role in episodic memories of the visuospatial type (including formation and consolidation), and memory optimization in sleep.^{163,164} It is possible that the impairment of this system may lead to behavioral impairment consistent with depression symptoms (e.g., changes in sleep and visuospatial memory impairment). This suggests that the depression symptoms and cognitive impairment associated with AD share a common underlying impairment of brain region as well as the neurotransmitter involved. Therefore, to disentangle the role of ACh, in relation to other neurotransmitters, in patients with AD and depression would be the next neurobiological avenue for research.

Other studies observed significant differences in the AD neuropathology (including neurofibrillary tangles and amyloid plaques) in the locus ceruleus, but not at the hippocampus or

EC, between AD patients with and without a history of depression.⁹² However, from a neuropathological perspective, the distinction of symptoms present in DSM depression from those of AD presents a challenge, given their heterogeneity. While no study explicitly examined the neurobiological differences between the DSM and PDC, even when there is a significant overlap between symptoms, there may well be unique neurobiological features associated with dAD.

Abnormal connectivity of the hippocampus to regions implicated in individual depression symptoms needs further examination. Substantial evidence exists to support the relationship between depression and morphological changes of the frontal lobes. For example, one postmortem study showed that patients with DSM-IV major depression had reduced glial density at the subgenual anterior cingulate cortex located at the frontal lobe.¹⁶⁵ Additionally, others have found lower cortical thickness at prefrontal regions in major depression by DSM-III-R relative to controls, due to a reduction in either the number or the size of the glia and as well as a reduction in neuronal cell dendrites.¹⁶⁶ Moreover, others with more advanced neuroimaging techniques have shown microstructural changes in the white matter at the frontal gyrus in individuals with late-life depression as diagnosed for major depression.¹⁶⁷ Aside from morphological changes observed in individuals experiencing depression, neurometabolic changes have been reported. For example, studies using Positron Emission Tomography imaging demonstrated that individuals with a diagnosis of probable AD and comorbid major depression, as examined by the use of the NPI and clinical interviews, had decreased glucose metabolism¹⁶⁸ and decreased regional cerebral blood flow in the frontal lobes compared to non-depressed patients with a comparable level of dementia.¹⁶⁹ Other sources of evidence, although at times conflicting, highlighted the change in the white matter (in terms of hyperintensity, as seen via

neuroimaging).¹⁷⁰⁻¹⁷² However, these results are controversial and the only probable link is to vascular depression, as several studies presented.³⁸ On the other hand, there exists a variation in terms of assessment and diagnosis of depression in these studies that to date no one study has highlighted as the aggregate limitation to understand the pathophysiology of depression in AD. In fact, the variability in the assessment and diagnostic approach here matters significantly, when a set of heterogeneous symptoms are required to label an individual as depressed. These individuals potentially present with differing underlying pathological impairment. Thus, future studies are needed to examine neurobiological markers of dAD via a homogeneous diagnostic criterion.

Currently, there is no globally accepted standard ("gold standard") for the diagnosis of major depression in AD. In fact it is suggested that the existing depression diagnostic criteria are still provisional.¹⁷³ Biologic tests, such as the dexamethasone suppression test, lack adequate sensitivity, specificity, or both, particularly in the setting of dementia. Similarly treatment response cannot be used as a diagnostic standard, because treatments differ and because not all depressed patients respond to treatment, even when it is adequately administered (also called "Ex juvantibus" fallacy¹⁷⁴). Depression, therefore, remains a clinical diagnosis based on an expert interview corroborated by clinical tools and collateral information. As a result, standardized diagnostic systems are needed in order to increase the validity and reliability of clinical diagnosis.¹⁷⁵

Neuropsychology of depression in AD and elderly without dementia

A diagnosis of depression can be complicated by concurrent dementia. For example, one early study showed that 2.6 to 3% of the patients are given an initial diagnosis of MDD were at a

subsequent follow-up were diagnosed with dementia.¹⁷⁶ The authors also indicated that those with initial diagnosis of depression and secondary dementia later were found to have a reversible dementia syndrome of depression. The diagnosis of 5 to 15% of those who had initial diagnosis of dementia were later changed to depression, and only 11 to 50% of those having initial diagnosis of dementia with secondary depression were given the same diagnosis at a subsequent follow-up.¹⁷⁶ These findings have been consistently reported by later studies.¹⁷⁷ Of note, additional comorbid conditions can complicate the diagnosis. In recent years there has been some hope that neuropsychological assessment may be helpful in facilitating diagnosis. The neuropsychology of depression has been an evolving field and been helping in A) prediction of future development of cognitive impairment leading to AD (potential risk factor); B) diagnostic differentiation; and C) detection of the lack of insight (also known as anosagnosia) in AD patients and thus informing on the fallibility of information emerging from the AD patients on the mood symptoms.

Thus the neuropsychology of depression in the non-demented late life individuals and individuals with depression in AD is briefly reviewed. Within this broad field it was thus necessary to focus on topics relevant for this thesis.

Late-life depression without dementia

Authors reviewing the literature regularly indicate that the neuropsychology of late-life depression is still poorly understood.¹⁷⁸ Studies examining cognitive dysfunctions in patients with late-life depression, have either used cross-sectional study designs, where depressed are tested and compared to non-depressed, or the neuropsychological scores of the depressed were compared to tests results of the normal individuals collected *a priori* as part of a test validation

(i.e., test norms). These studies suggested that the neuropsychological impairment in late-life depression [diagnosed (mild to moderate)] is characterized by decrement of attention and recall.^{85,179} These domains are mostly associated with frontal executive malfunctioning system.¹⁸⁰ Additionally, few others highlighted the paucity of speech with longer latency in older adults with MDD.²⁵ Impairment of language functioning, visuospatial recall,^{181,182} subjective memory impairment,^{183,184} short-term memory,^{185,186} attention, and concentration³¹ have been reported to a lesser extent. Evidence also indicates dysfunction of multiple cognitive domains in older adults with depression. In older individuals with depression presenting with cognitive deficits, executive dysfunction, diminished episodic memory functioning (e.g., on learning and recall on California Verbal Learning Test, CVLT), and slower speed of processing functions (also called central processing speed) have been the most prominent of the cognitive functions and consistently reported.

Robbins and colleagues highlighted the impact of motivation as assessed by the test of computerized test of delayed matching to sample (DMTS) and exaggerating negative response to failure as a contributing reason for overall cognitive deficit.¹⁸⁷ But, later cross-sectional neuropsychological studies suggested that by controlling for motivation and speed of processing, the executive impairment remains the core neurocognitive deficit differentiating older adults with depression from without,¹⁸⁸ which is consistent with the suggestion by Alexopoulos and colleagues that mainly executive abilities influence the course of geriatric depression.⁷¹ The implications of the executive functioning thus is of particular interest, given that executive dysfunction has been associated with the lack of insight in dementia.¹⁸⁹ This factor plays a significant role in testing older adults suffering from both AD and depression, which will be discussed later. Noteworthy that others have postulated the presence of other types of depression

in geriatric population with distinct neuropsychological maps including “vascular depression” with mixed neuropsychological deficits⁶⁹ or “depression without sadness” presenting with psychomotor slowing.⁷⁰ These facts inform us on the various presentation of depression in older adults; yet they remain to be validated.

To complicate matters, depression in older adult has been suggested to be a prodromal manifestation of AD and even as a non-biological marker of late life dementia.⁵⁴⁻⁵⁶ For instance, depression presenting as a potential risk factor for AD is seen in a retrospective study of 243 AD patients.⁵⁵ AD patients, but not healthy controls, had a higher premorbid depression. In this study, a geriatric psychiatrist accessed and gathered information from the informant on patients’ history, and depression symptoms were measured using the Cornell Scale for Depression in Dementia (CSDD) cut-off scores of 7 for DSM-III-R, in order to diagnose depression. Others though refuted the idea that depression may predict later development of probable AD. Of note, this study examined depression by the GDS,¹⁹⁰ which is different approach to assessing depression from the earlier study. This shows heterogeneous approaches in assessment of depression in these studies, which renders decision-making regarding depression being a potential risk factor for later development of AD.

Depression in AD- diagnostic differentiation

Memory loss seems to be present in both depressed older adult and those with dementia.¹⁹¹ When dementia co-occurs with depression in older adults, differential diagnosis of clinically depressed older adults without dementia from those with early signs of dementia becomes a major concern.^{192,193} The neuropsychiatric syndrome of depression mimicking dementia, the so-called “*pseudodementia*” has been known to complicate diagnosis and treatment planning.¹⁹⁴

The literature on *pseudodementia* goes back to the 19th century and again in the late 1970s to early 1980s.^{194,195} In recent years the term “dementia syndrome of depression” seems to have replaced this term.¹⁹⁶ Nowadays, the prevalence of this diagnosis has been substantially lowered given the advances in differential diagnosis, and a range of clinical utility (e.g., EEG) available to clinicians.

Unfortunately the results of neuropsychology of depression as diagnosed by DSM criteria or via assessment scales in AD are showing substantial variability. For example, Cummings stated that depressed AD patients do not exhibit greater impairment of attention, language, memory, or visuospatial functioning than patients without depression.¹⁹⁷ Interestingly, studies tapping into individual cognitive function, showed no significant difference between groups in terms of episodic memory (free-recall and recognition), and short-term memory (digit span forward and backward). Also no significant difference was observed on global cognition as assessed by the MMSE [depressed: 19.33(5.68), n=9; non-depressed: 19.62(3.26), n=45] (free recall, recognition, and digit span).¹⁹⁸ This result has been consistently demonstrated by other studies yet without specifying AD severity. For instance, an earlier longitudinal study¹³⁷ with probable AD patients as diagnosed by the McKhann criteria,¹⁹⁹ and meeting DSM-III-R major depression diagnostic criteria, found no significant difference in the neuropsychological profile of AD patients with (n=10) and without (n=10) depression. This study used a comprehensive neuropsychological battery assessing for memory, learning, problem-solving, expressive and receptive language, visuospatial, visual discrimination abilities, and speed-attention. Of particular interest, they have used the trail making test, part B, for assessment of speed of processing attentional ability, and controlled for the level of general cognitive functioning as assessed by the MMSE, age, education, and duration of dementia illness. In contrast to studies

reporting non-significant difference between groups, other studies suggested that cognitive impairment in the early stages of AD with co-occurring depression is more severe than patients with depression alone, and that is in nearly every cognitive domain.^{200,201} Moreover, others pointed that depression in AD tends to alleviate general intellect as assessed by the Wechsler Adult Intelligence scale.²⁰² There are studies indicating that the pattern of cognitive impairment in dementia patient with depression may differ from those with dementia alone. In these studies, cognitive decline has been found to be progressive and faster, and tends to subside or stabilize once depression is treated.²⁰³

However, there is a common acknowledgment in the literature that depression in moderate to severe AD is hard to disentangle from symptoms of dementia and that depression become parts of the behavioral changes associated with moderate to severe AD.²⁰⁴ As a result of which little has been documented to show differentiation of AD patient with moderate to severe cognitive impairment with and without depression, and majority of the evidence emanate from the very mild to mildly moderate cognitively impaired AD patients.

Earlier studies have shown that AD patients with depression have more psychomotor retardation, confusion and general apathy-like symptoms.²⁰⁵ However, overall studies examining neuropsychological differences between AD patient with and without depression showed mixed results. For example, one study using Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale (WMS) observed no significant difference between groups on the subtest of the scales;²⁰² whereas another group using the MMSE showed a significant difference, in that depressed had lower MMSE score than the non-depressed [depressed: 9.5 (6.7), n=24; non-depressed: 13.3 (6.4), n=120; p-value= 0.01].²⁰⁶ This study used the DSM-III-R major depression diagnostic criteria, and AD was ascertained using the McKhann diagnostic criteria (1984). Few

years later, another study examining neuropsychological performance in probable mild AD patients with and without depression (diagnosed using the DSM-III-R criteria) showed no differences on a series of tests assessing memory, language (expression and receptivity), visuospatial functioning and speed-attention, or rate of cognitive decline.²⁰⁷ It is noteworthy that the groups in this study were balanced for MMSE scores at baseline, which may affect their results in detecting significant differences between groups [depressed: 21.3(2.3), n=10; non-depressed: 21.4(2.2), n=10].

On the other hand, a cross-sectional study contrasted neuropsychological performance of very mild to mild-AD patients with (n=7) to without (n=41) depression and found that there is a significant difference between very-mild AD and mild AD with depression on WMS tests of logical memory, mental control, associate learning (recall) for total and subscales, digit backward, verbal fluency (s, p, and total), Boston naming, Boston visual retention test, WAIS (information, block design, and digit symbol), Trail Making Test (seconds), and crossing off.²⁰⁸ In all tests, depressed under-performed suggesting of the global cognitive impairment in depressed with mild AD. In the contrary, comparison between mild AD with depression (n=7) and without (n=66) showed a clear significant difference only on tests of WMS digit backward, word fluency (s, p, and total), WAIS block design and digit symbol, trail making, and crossing-off. This study shows that tests relying on speed of processing (e.g., trail making in seconds, and verbal fluency) are more affected by depression. In this study, AD was diagnosed based on the McKhann diagnostic criteria (1984) and depression was diagnosed using the DSM-III and Feighner diagnostic criteria for primary affective disorders (including for depression),²⁰⁹ the precursor to the RDC. Groups were balanced for age, education and socioeconomic status. In sum, the result of this study shows that it is much harder to differentiate depressed from the non-

depressed in mild-AD than very mild-AD, and tests capturing speed of processing or global cognitive functioning should be more sensitive for differential diagnosis purpose.

In contrast, a cross-sectional study²¹⁰ showed non-significant differences between depressed and non-depressed probable mild AD patients in terms of MMSE scores [depressed: 17.2(7.5), n=24; non-depressed: 18.4(6.0), n=50] and 13 other neuropsychological measures. Of substance, although non-significant, the depressed in comparison to the non-depressed under performed on tests of trail making test and tests that are sensitive to attention function and speed of cognitive processing. In this study depression was diagnosed using the DSM-III-R major depression criteria with Hamilton depression rating scale, and AD was diagnosed using the McKhann diagnostic criteria (1984). Of note, another group that used a battery of 13 neuropsychological tests to show the difference between depressed (n=37) and non-depressed (n=98) probable AD patients obtained similar results.²¹¹ There was no significant difference between groups in terms of global cognition as assessed by MMSE [depressed: 21.3(3.8), non-depressed: 21.6(3.6)]. Particularly, however, they found WAIS-R block design and digit symbol, and speeded motor program to be the differentiating scales, where AD with depression under performed on this tests in comparison to AD without depression. Of essence, the groups in this study were balanced on age, education, and overall severity of dementia, and patient's diagnosis for depression as ascertained using the GDS scores. As for AD, diagnosis was accomplished using the 1984 McKhann diagnostic criteria.

Consistent with impairment seen in older adults with depression, cognitive impairment in AD with depression is mediated by effortful processing,²¹² which is potentially due to the lack of motivation (maybe confounded by apathy), or severity of disease.

In terms of dAD, only one study examined depressed probable AD patients versus non-depressed patients via comprehensive neuropsychological assessments.²¹³ This study found no significant difference between PDC positives and negatives in terms of scores on the WAIS-R, Wechsler Memory Scale (WMS-R) (Logical memory I, Visual reproduction I) and the Rey Auditory Verbal Learning Test (RAVLT). Additionally, in contrast to the PDC negatives, the PDC positives took a longer time to complete the Part B of Trail Making Test ($p < 0.001$), a test sensitive for cognitive flexibility and divided attention. Subsequently, a significant difference was observed between groups in terms of the score obtained by subtracting the time taken to complete the Part A from the Part B of the Trail Making Test ($p < 0.001$) suggesting of a slower reaction time. Moreover, consistent with earlier studies, this study found no significant difference between groups on global cognition as assessed by the MMSE. This study concluded that the PDC positives, but not negatives, showed greater impairment of attention and executive functions, specifically pertaining to divided attention; however, validation of the PDC is warranted for future studies.

In sum, the neuropsychology of depression in AD is complex, and has seen signs of variability on how depression was defined or assessed, and at what level of cognitive impairment depression was present. Given the heterogeneity of results, experts suggested that neuropsychological assessment attempting at differentiating AD patient with depression from without are not always fruitful. Thus treatment with antidepressant was recommended as a tool helping differential diagnosis (the so called “Ex juvantibus” approach/fallacy).²⁵ From the shown overview of the literature, one can positively say that there are mixed results in terms of what helps differentiating AD with from without depression for all cognitive level of severities.

However, speed of cognitive processing and extent of executive impairment can be highlighted as the most significant differentiating factor for mild cognitively impaired AD.

The following section will facilitate better understanding of the utility of neuropsychology in differential diagnosis of AD patient with or without depression in the relationship between insight and depression in AD.

Insight and awareness of symptoms

Awareness of cognitive deficits in AD has been reported in several studies,^{214,215} however its relationship to psychiatric symptoms, or precisely to depression has not been well examined. Studies of anosognosia (also called the lack of insight, unawareness of illness, illness of “aperception”, or the “aperception” of one’s illness) in AD examining psychiatric moderating factors such as depressive symptoms have shown inconsistent results, in that some report a positive relationship between depression and the lack of insight, while others report a negative relationship. In fact, a review examining both neuropsychological and neuroanatomical aspects of unawareness of illness in AD suggested the lack of clear relationship between disturbance of awareness and cognitive/affective symptoms in AD²¹⁶ where some authors suggested that awareness of psychiatric and behavioral syndromes are better preserved than cognitive symptoms in AD patients.^{217,218} Besides, no study examined awareness in light of dAD.

Several authors proposed that the awareness of dementia does not appear to be associated with the risk of depression as assessed by HAMD.^{219,220} For example, a 2013 study on anosognosia and depression in 49 AD patients as diagnosed by the 1984 McKhann diagnostic criteria showed a non-significant yet negative, but very small correlation between scores on the GDS and Anosognosia Questionnaire for Dementia (AQ-D)($r=-0.04$, $P\text{-value}>0.05$); however a

significant and larger positive correlation was obtained with the NPI depression item ($r=0.53$, $P\text{-value}<0.01$).²²¹ Additionally, a medium and significant yet negative relationship was observed between the scores on the AQ-D and MMSE ($r=-0.45$, $P\text{-value}<0.01$). The MMSE scores ranged between 8 and 28 (mean=19.66, SD: 5.88). Of note, higher positive score on the AQ-D suggests the lesser insight, higher score on the GDS suggests the presence of depression/depressive mood for the past week, and higher the score on MMSE suggests better global cognitive performance. Thus, these results suggest that A) higher the cognitive impairment, lower is the insight; and B) that the correlation between depressive mood/depression and insight was scale dependent. However, it is important to note that, the larger correlation between NPI and AQ-D versus GDS and AQ-D is maybe due to the fact that NPI gathers information from caregiver, and similarly, the smaller or the non-existent relationship between GDS and AQ-D is due to the fact that GDS is a self-reported screening questionnaire.

On the other hand, several studies showed an inverse relationship between depression and the lack of insight. For example, a cross-sectional study examined the correlation between the level of insight and depression and cognitive impairment in 91 AD patients.²²² By using the Neurobehavioral Rating scale (NRS) to assess both depression and level of insight, this study found that, as the level of insight increases, depression symptoms increases. Also they found an inverse relationship between the illness severity and insight. Of interest, the MMSE score for the AD patients enrolling in this study were heterogeneous (score ranged between 0 and 28, mean = 11.8), suggesting that potentially a significant number of patients were suffering from moderate cognitive impairment. Additionally, one study showed that in 84 probable AD patients, anosognosia was negatively correlated with both global cognition as assessed by MMSE ($r=-0.364$, $p\text{-value}<0.001$, range was between 4 and 28, mean = 19.5, SD = 5.0) and depression

symptoms as assessed by GDS ($r = -0.294$, $P\text{-value} < 0.05$)), but no significant relationship was found with NPI dysphoria item ($r = -0.149$). Moreover, this study has shown the lack of positive association between AD severity and insight.²²³ Although this study examined other predictable neuropsychological correlates by a battery of tests assessing memory, executive, and attentional abilities (e.g., Trail making tests, Stroop, WCST), only response inhibition, a correlate of executive control, as assessed by the part III of the Stroop test was associated with anosognosia. Of note, this study used the adapted Japanese anosognosia scale to examine anosognosia and defined the terms “anosognosia” as the lack of recognition of the illness. Other recent studies also reported similar results. For example, one study examined the relationship between insight, psychiatric disturbance and AD.²²⁴ In this study, probable AD was ascertained by the McKhann criteria¹⁹⁹ in 107 outpatients; and a clinician-rated scale, the NRS,²²⁵ on the other hand assessed depressed mood and insight. They found that insight was significantly predicting depressed mood even after controlling for global cognition (MMSE range: 9 to 28, mean = 19.4, SD = 4.7); where greater insight was found to be associated with depressed mood ($\rho = 0.21$, $P\text{-value} < 0.05$). They concluded that insight may be differentially related to mood symptoms within AD, such that patients with intact insight are more depressed.²²⁴ This result is consistent with another recent cross-sectional study of anosognosia that examined the reason for discrepancy between ratings of the quality of life by the patient versus the caregiver. This study also found an inverse relationship between anosognosia as assessed by AQ-D and depression as assessed by the GDS.²²⁶

The literature on the lack of insight and its correlation with neuropsychological impairment and test validity is complex; nonetheless, evidence marshaled to highlight executive and general cognitive dysfunction as a significant neuropsychological correlate of unawareness in AD, that

are similarly effected by depression. For example, a review examined neuroanatomical and neuropsychological studies and highlighted the impairment of the right frontal and right temporal/parietal lobes as the anatomical correlate, and global cognition, memory, and executive as neuropsychological correlates of anosognosia.²¹⁶ This review showed consistency between function and neuroanatomical impairment in AD patients with anosognosia, now consistent with recent neuroanatomical findings.²²⁷ Of note, the recent neuroanatomical study by Zamboni and colleagues (2013) did not find a significant correlation between the level of insight and GDS score in 17 probable AD patients ($r=0.05$), MMSE score ($r=0.09$), Hopkins verbal learning test (episodic memory, $r=0.26$), Category fluency (semantic memory, $r=0.17$), MoCA delayed recall ($r=-0.08$), and other subscales of the MoCA for executive functioning.

In sum, it is imperative to acknowledge that no study examined the lack of insight in light of the PDC-dAD. The literature is confounded by the use of mixed terminology/conception of the condition, heterogeneous prevalence and AD sample included in the studies, and the scales used to capture the phenomenon. The latest review implicitly highlights multiple terms (e.g., the lack of self-concept, insight, awareness, and perception of the impairment) to show how the literature is confounded by the mixed terminology.²²⁸ Furthermore, this review pointed to the heterogeneity of findings in terms of the level of awareness in AD and its relationship with cognitive/ behavioral symptoms, and the lack of clear association between awareness and neuroanatomical correlates.²²⁸ Moreover, discrepancy exists as how the level of insight was ascertained, for example some report the difference between patient and informant rating whereas others use an actual objective measure of insight via an assessment scale. The discrepancy in the relationships between the depression scales and anosognosia assessment scale suggest the lack of clear conclusion about the correlation between depressive

symptoms/depression and the level of insight; however, given the relationship between global cognition and the level of insight, it is more likely that the patients are under-reporting or have the insight to report depressive symptoms. Additionally, no study to date has examined the magnitude of difference between informant rating of patient without cognitive deficit and the patients. Thus it is hard to determine, how much of the difference between scores reported by the informant and the patient is actually due to patient having limited insight versus the difference being only natural given individual variability.

In essence, depression in older adults with and without dementia is prevalent with a negative stigma around its prognosis. Its neuropsychological data shows signs of heterogeneity in terms of which cognitive domain is more dysfunctional, which brain regions are affected, and to what extent. Moreover, multiple diagnostic criteria exist to classify depressed older adults. It has multiple risk factors and its etiology is not well understood. Moreover, the variability in the results pertaining to studies of insight and depression, and differential diagnosis via a neuropsychological assessment, only suggests that a better diagnostic approach to depression and its assessment may be needed to minimize this heterogeneity. In sum, depression in older adults is a significant burden on society and complicates normal aging. These factors together ensue a need for studying depression in older adults from screening, diagnosing and assessing, to prevention, treatment, and its management to hinder these devastating costs. Here, we will try to shed light on diagnosis, assessment, and treatment aspects of depression in older adults with dementia of the AD type.

Pharmacotherapeutic approach to depression in AD

For treatment of depression alone, SSRIs or a Serotonin-Norepinephrine Reuptake Inhibitor

(SNRIs) are the psychotropic of choice. For individuals with AD and co-morbid depression, a trial of an antidepressant, preferably of the type SSRI, SNRI, or Norepinephrine Reuptake Inhibitor (NRI), could be initiated. These classes of medications are prescribed either alone or in combination.²²⁹ Pharmacotherapeutic guidelines for treating depression in AD recommend that pharmacological treatment with minimal and least severe adverse events be used as a first-line approach.^{230,231} The recommendation issued by the Canadian Consensus Conference on Dementia (3rd CCCDTD)²³² is that if a person with dementia and depression has an inadequate response to non-pharmacological interventions, a trial of antidepressant treatment should be considered with preference for an SSRI. However, there is a lack of consensus regarding which depression scale/s to use for assessment of depression in AD. Current clinical trials are either using the DSM or the PDC-dAD with an array of outcome measures with mixed validities. Given the uncertainty regarding which scale to use in AD – whether to use a patient rating scale, or to interview the patient, caregiver or both – or which criteria to use for the diagnosis of depression in AD,^{9,233} it is difficult to achieve an important treatment goal in AD, and to minimize factors exacerbating cognitive impairment and hindering the efficacy of therapeutic interventions, such as depression.²³⁴ Since the 1980s,^{235,236} treatment guidelines have improved; yet individuals suffering from cognitive impairment and co-morbid depression may not have fully benefitted from pharmacotherapeutic approaches.²³⁷ At times, depressive symptoms improve somewhat but the global cognitive impairment remains.²³⁸ These facts generally reinforce the idea that the pharmacotherapeutics of depression in AD will greatly benefit from consensus on diagnostic criteria and from well-validated scales. If these were in place, findings from trials could be more readily interpreted than at the present time. For example, the result of a meta-analysis that I have performed using the consensus-based Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) statement²³⁹ could have been different if we had homogeneous assessment scales and diagnostic approaches in the included trials. The study was set primarily to examine the effect of SSRI treatment on depression and cognition in AD with diagnosed co-morbid depression, and secondly to highlight gaps in the literature.²⁴⁰ Four of the included studies used the DSM and one used the PDC-dAD as diagnostic criteria. These studies used multiple depression measures including the CSDD and the HAM-D. There was a difference in the effect-size estimates for the depression scales.²⁴⁰ Both analyses included studies with DSM- and PDC-based diagnosis of depression. In sum, this study suggested that the intriguing difference in the effect sizes could be explained by moderating factors, such as assessment approaches (see Appendix N). This work was then followed by a letter to the editor of the Lancet in response to a large European antidepressant clinical trial and stated that a real necessity for antidepressant use must be established, and criteria for application should be developed.²⁴¹ It is only pertinent to say that diagnostic approaches used in those studies do not seem to capture the same depression in patients with AD, and the outcome measures have dissimilar constructs. Additionally, the method of gathering information about symptoms from these outcome measures varies. More importantly, at the time of trials, none of the assessment scales were validated for the PDC, and thus a different cutoff score would have been needed to confirm treatment effect. This variability in assessment and diagnosis, and the use of non-validated cutoff scores, could account significantly for the lack of an observable clear benefit of antidepressant treatment for depression in AD, which further underscores the need for the current research that examines the utility of depression scales in dAD.

Depression assessment scales for Alzheimer's disease

As previously mentioned under the depression assessment scale for the elderly section of this work, there are a plethora of depression scales in existence,^{107,108} and their utility is dependent on the context in which they are used. Based on factors including the administration method, response format, complexity, and purpose of each scale, it is currently not straightforward to determine which scale/s should be used for the assessment of depression in dementia. The existing dementia scales either perform sub-optimally or do not really do much better than scales used with the general population or for older adults. In other words, their practicality is limited. Current evidence shows that few scales have been specifically designed for dementia (e.g., the CSDD)¹¹³; and there are scales designed to capture information from both the patient and the informant regarding the patients' symptoms (e.g., the Cambridge Examination for Mental Disorders of Elderly [CAMDEX]¹¹², the CSDD). Scales developed for older adults use multiple response formats, or are differentially administered, such that one is self-administered versus another that is given by a clinician (e.g., the GDS-30 vs. the HAM-D, respectively). The variability in the type of scales, duration that it take for administering them, the complexity of the scale, how it is administered, and how the responses are collected, make test selection for screening depression in AD particularly challenging. To date, there is no guideline on which scale to use for screening depression in AD. Questions such as, what length of screening scale is appropriate for their level of cognitive impairment, which response format is ideal, and whether we should rely on the patient, informant or both, are looming large, which require addressing.

Among the scales facilitating diagnosis, none exists that is short and specific for AD patients, and there is no scale that is PDC-based. Thus, with regards to screening of dAD, we have several concerns. First, the majority of the validated scales for PDC are time consuming, cognitively

taxing, and in part confounded with somatic symptoms. Second, it is not clear whether we should rely on the patient or informant report of symptoms. Third, scales developed for older adults that are short and easy to administer with comparable informant-based version providing collateral information are not validated for PDC. These are significant gaps in the literature that prompt evaluation of the utility of specific depression scales with regards to PDC-dAD. In sum, these are points that will be discussed here shortly.

The majority of scales for assessment of depression in dementia are relatively time-consuming (roughly 20-60 min) and are interview based, which may not be optimal for use at differing levels of cognitive impairment or for routine easy screening in clinics. In fact, the Montgomery–Åsberg Depression Rating Scale (MADRS), a clinician rated scale assessing change in the severity of DSM depression symptoms, not specifically designed for dementia, and the CSDD, an interview based-instrument to assess signs and symptoms of depression in dementia, but not specific to AD, were examined and recognized as valid for use against the PDC-dAD.¹⁵⁵ Yet, they remain long and time consuming and cannot be readily administered as a screening measure.

It is important to consider a well-established pattern in dementia, that patients under-report (false negative) and informants over-report (false positive) depression symptoms.²⁴²⁻²⁴⁷ The discrepancy between the false negative and false positive can be problematic given that there is no guideline as to how much weight should be allocated to each report. Currently, there is a lack of consensus with respect to depression measures in AD, and it is not clear whether patient, caregiver, or both should be interviewed. This complicates interpretation of treatment outcomes. Patients with more severe cognitive impairment and lower functioning may need more of the informant input, in contrast to patients with milder levels of impairment who would be able to

accurately respond to an interview or be able to fill out a questionnaire. Moreover, given that roughly 15%²⁴⁸ of individuals with mild AD are also sustaining anosognosia (the patients' lack of insight into their symptoms and circumstance), the presence of informant input may help to ameliorate the sensitivity of depression diagnosis, and eventually get us closer to the actual prevalence of depression. It is noteworthy that the need for patient input in the assessment of depression in AD has simply not been studied sufficiently. This absence of a consensus can be readily seen in clinical trials and epidemiological studies, and may be a significant source of heterogeneity in treatment outcomes²⁴⁹ and prevalence range, which requires further examination.

Given the heterogeneity in the level of cognitive impairment and insight for the AD population, to assess depression, an ideal scale may be one that is short, has a low level of complexity with an easy response format, and possibly incorporates both patient and informant input. These facts highlight the need for examination – content validity via experts' judgment and concurrent validity against other assessment scales. In short, these allow selection of a short, easy to administer, less cognitively taxing older adults screening scale with comparable informant version for use with the PDC. In addition, the combined examination methods should provide optimal validity, and a direction for selection of a depression screening scale for use with the PDC. Potentially, this may help better screening of depression in AD, before applying the PDC, or simply to select a scale for use in conjunction with the PDC to minimize both false negatives and positives at diagnosis.

The following chapters will attempt to shed light on some of the issues concerning diagnosis and assessment scales for use with demented older populations. Particularly, the next chapter will review the evidence in support of the PDC's validity as the gold diagnostic standard for use

with AD. Subsequent chapters will help to delineate which depression screening scales works best in the detection of dAD according to the PDC, and whether patient- and informant reports work equally well. Additionally, given the challenges (e.g., various level of cognitive impairment and insight) in asking patients with AD about depressive symptoms, and the fact that the GDS-30 is the most administered scale and pre-dates the GDSIF-30 and the HDS-OA, a content validity study focusing on the GDS-30 will be conducted. This will examine whether experts rate the GDS-30 the same way or recommend that a revision is direly needed.

Chapter 3. Study 1- Comprehensive systematic review and meta-analysis gauging the validity of NIMH-PDC defined depression of AD

Synopsis

This systematic review and meta-analysis examines the support for the validity of the National Institute of Mental Health - Provisional Diagnostic Criteria of depression of Alzheimer's Disease (PDC-dAD). The PDC-dAD were formulated to recognize depression in Alzheimer's disease (AD), which is under-reported and not well identified by the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for major depressive disorders. I have reviewed clinical evidence from epidemiological studies on AD and depression that compared the two criteria (DSM and PDC), as well as from antidepressant randomized clinical trials using the PDC. Additionally, I have examined the validity-evidence (e.g., psychometric data) on PDC. The aggregate evidence reviewed here suggests that depression co-occurring with AD differs from other depressive disorders as defined by the DSM. Additionally, it appears that the PDC are the best standard available today to facilitate diagnosis of depression in AD. This notwithstanding, critical questions remain for future research, specifically on the phenotype of depression of AD. These questions are particularly important in light of the inclusion of neuropsychiatric symptoms in the 2011 National Institute on Aging – Alzheimer's Association diagnostic framework for all-cause dementia, and the emerging Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-V) where diagnosis of dementia has been substantially revised.

Background

The Diagnostic and Statistical Manual of Mental Disorders (DSM) revised fourth edition was developed to aid in the diagnosis of major depression in the general population. However, it does not address the challenges of diagnosing depression that is comorbid with AD. It has been suggested that older adults with dementia and depression present with different symptoms than those included in the DSM-major depressive disorder (MDD). Moreover, differentiation of depressive symptoms from dementia is difficult and complicates the patients' prognosis. Thus, different from both DSM major and minor depression, the PDC were formulated to enable better recognition of depression specific for AD.¹⁰

There was recognition by an expert panel of 21 members from geriatric medicine, geriatric psychiatry, neurology, and neuropsychiatry, all with extensive research in dementia care and late-life depression, that the severity of signs and symptoms of depression in AD are milder and that it encompasses a wider range of symptoms than MDD.¹⁰ The panel was convened for a workshop to address the heterogeneity in the epidemiological data and “to garner a therapeutic claim from the Food and Drug Administration (FDA)”.¹⁰ Furthermore, they posited that the difference between dAD and MDD may involve the incidence and prevalence, history of depression (patient or family), frequency and duration of symptoms, suicidality, outcomes and therapeutic responses. The description of symptoms in the PDC is phrased to avoid possible confounding of symptoms due to dementia such as diminished function, language, and cognitive abilities in AD. The PDC require three symptoms instead of five for diagnosis of depression, and symptoms do not need to be persistently present for a 2-week time. Similar to MDD, at least one of depressed mood or anhedonia (decreased positive affect or pleasure) is required for the PDC.

The MDD item of diminished ability to think or concentrate is dropped.⁹ In turn, irritability, and social isolation/withdrawal are added items.

The PDC are different from the DSM, and since their inception experts have repeatedly advocated for the examination of their validity.^{131,143} Therefore, we have employed accepted evidence-based methods (a comprehensive review and meta-analysis) to examine the validity of the PDC.²⁵⁰⁻²⁵² This appraisal starts by examining the prevalence of depression determined by the PDC and its potential modifiers and subsequently exploring the characteristics of subjects meeting the PDC, including their meeting DSM criteria, symptoms endorsed, and rate of suicidal ideation. My expectation was that among those meeting PDC criteria a proportion would also meet DSM criteria whereas others would not given the symptom overlap. Furthermore, the performance of assessment scales, and their utility in SSRI clinical trials is examined. Greater improvement in patients diagnosed with the PDC compared to those diagnosed with DSM would in my view provide support for the validity of the PDC. When possible, evidence emanating from PDC studies will be compared with evidence on DSM-MDD. In light of the comprehensiveness of the review, other evidence that emerges and anecdotal notes will be included where appropriate.

Methods

For the purpose of a comprehensive review, a literature search was conducted to assess the number and type of published studies on the PDC. Medical electronic search engines (PubMed and EMBASE) were queried in the first week of November 2013 (updated in January 2015) using “provisional diagnostic criteria for depression of AD” as the key term for independent original studies without language limitations. For both engines, no limitation was imposed about

the language or the type of study. The “related citations” function in PubMed was used as a crawler to examine for possible studies failing to meet our search criteria. For EMBASE, only the keyword search tool was used to carry out the search. The bibliography sections of the retrieved published papers meeting our *a priori* set selection criteria were subsequently examined for additional studies. Within the systematic review, with defined criteria for conducting a meta-analysis based on the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines,²⁵³ and Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for assessment of cross-sectional observational studies,²⁵⁴ the evidence for prevalence of depression of AD (dAD) as diagnosed by the PDC was evaluated. The inclusion criteria for the meta-analysis were: 1) diagnosis of AD according to the 1984 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria,¹⁹⁹ and 2) evaluation of depression prevalence by the NIMH-PDC and by at least one other diagnostic criterion. Exclusions of studies were based on A) including mixed or non-AD dementia; B) duplicate published data; and C) case-series.

Data were extracted by me and subsequently reviewed by two research assistants independently for accuracy. For all eligible studies, inferential and descriptive statistics and prevalence were retrieved. Median and prevalence estimates [Event Rate (ER)] were calculated for depression according to the PDC and for other comparable diagnostic criteria and assessment scales. Subsequently, the prevalence estimates were pooled to derive an omnibus effect-size estimate (ER) at 95% confidence intervals (CI), and to allow examination of the confounding *a priori* selected factors [age, sex, and MMSE²⁵⁵] on the slope of the ER via meta-regression using method of moment (also called the DerSimonian and Laird approach).²⁵⁶ The funnel plot method

was applied to examine for publication bias. Comprehensive Meta-Analysis (CMA: Ver. 2.0)²⁵⁷ served as the statistical platform for all meta-analytic evaluations and graphical presentations. We anticipated that a full examination of heterogeneity would not be possible because of anticipated differences in study design, population, and outcomes;²⁵⁸ however, the corresponding Q-values and I^2 values were investigated. Where appropriate and with available data, an aggregate measure in terms of Hedges' g or Cohen's d was generated for examination of the group differences in terms of diagnosis. Consistent with other meta-analysis²⁵⁹ for the graphical representation and meta-regression analyses, the point prevalence rates at the 95% CI were transformed.

To compare depression prevalence rates from the PDC to the DSM or the International Classification of Diseases (ICD), using binary data (e.g., PDC positive, PDC negative versus DSM positive, DSM negative) an Odds Ratio (effect-size) was calculated via the CMA. For the aggregate overlap between PDC and DSM-MDD, an average was calculated for PDC alone, PDC+DSM, and DSM alone from the included studies, and subsequently a chart was developed to present the percentage of overlap between diagnostic criteria.

For assessment of the frequency of individual PDC symptoms, when reported, data were retrieved from graphical representations and subsequently compiled for analysis. For retrieval of the data from graphs, two raters (Amir A. Sepehry and Philip E. Lee) independently rated the graphs for reported frequencies and subsequently averaged the frequencies before inclusion into the final analysis.

To complement our comprehensive systematic review of the validity-evidence for the PDC, bibliographic sections of the emerging studies were examined for psychometric studies, SSRI trial evidences, reviews, and extra notes.

Results

Description of the included studies

The search of the electronic literature yielded six observational studies with AD, four of which were independent to allow examination of the prevalence for depression,^{134,152-154} and one different from the other four, was a case-series. From the six studies, three independent observational studies, but not the case-series study, reported data to run an aggregate measure for assessment of diagnostic agreement.^{134,152,260} Similarly, three studies reported sufficient data to run an aggregate measure on the PDC symptoms.¹⁵²⁻¹⁵⁴ For the use of the PDC in clinical trials, an ad-hoc search using both controlled and uncontrolled vocabulary revealed 3 extra studies. Further examination of the literature showed 2 comparative studies with AD patients, 6 reviews and 1 book chapter on depression in AD also discussing the PDC. Table 1 shows the list of all publications available to date (N=23) that used the PDC for diagnosis or in review.

Table 1. Published seminal works (N=23) examining the PDC in AD or dementia-spectrum

Studies	Observational	Comparative	Clinical trial	Review	Book Chapter
<i>AD</i>					
Rosenberg et al. 2005*	X				
Vilalta-Franch et al. 2006	X				
Teng et al. 2008	X				
Large-Barca et al. 2010	X				
Engedal et al. 2011	X				
Chiu et al. 2012	X				
Nakaaki et al 2007		X			
Lee et al 2006		X			
Strakstein et al. 2005**			X		
Rao et al. 2006			X		
Munro et al. 2010 (for DIADS-2)			X		
Banerjee et al. 2011 (HTA-SADD)			X		
Lyketsos & Olin 2002				X	
Lee & Lyketsos 2003				X	
Amore et al. 2007				X	
Starkstein et al. 2008				X	
Panza et al. 2010				X	
Geda et al 2013/Smith et al 2013				X	
Richly et al. 2012					X
<i>Dementia (mixed) or MCI</i>					
Leontjevas et al 2009		X			
Verkaik et al. 2009	X				
Leontjevas et al 2012		X			
da Gloria Portugal et al. 2012	X				

Note: *Case series; **Non-specific to PDC

Prevalence of depression by PDC and DSM

Four independent observational (prospective and retrospective) studies (N=4) reported prevalence for depression in AD including possible and probable AD, with Mini–Mental State Examination²⁵⁵ scores ranging from 0 to 30, using more than one diagnostic approach. These studies were carried out in various settings (e.g., hospital, nursing home) with the majority of the participants being female (range 55.8 to 70.9%), with an average age ranging from 75.2 to 83.^{134,152-154} These studies provided data from Norway, Spain, Taiwan, and the United States. From these four studies, the majority reported AD patients attending outpatient clinics, with an exception of one study,¹⁵³ which included both nursing home and geriatric psychiatry patients. The calculated median for the prevalence rates for depression by the PDC was 36.9%.^{134,152-154} In turn, the prevalence by the DSM-MDD ranged from 9.3 to 34.8% (median 13.7%). One study showed that the prevalence of depression by DSM minor depression alone was 22%.¹⁵² In 3 studies,^{134,153,154} the prevalence by the International Classification of Diseases (ICD) was 4.9 to 47.3% (median 17.5%). In 3 studies,^{134,152,154} the point prevalence (PP) by the Neuropsychiatric Inventory (depression or dysphoria [NPI-Q] endorsed) ranged from 43.7% to 54% (median 50%). Other measures were inconsistently used and reported prevalence of 9.8 to 49.7%. Finally, in one study, PDC-dAD showed a higher prevalence (44%) when compared with the DSM-established cutoff scores for screening measures such as the Cornell Scale for Depression in Dementia (CSDD) (30%) and the Geriatric Depression Scale (GDS) (33%), and a lower rate compared to the NPI-Q depression item (50%) (see table 2).¹⁵²

Table 2. Description of the epidemiological studies examining PDC

Studies	Location	Total n	Diagnostic criteria (Prevalence)			Scales	Demographic		
	Country/Setting		PDC- dAD (%)	DSM- MDD (%)	ICD (%)	Depression scales (%)	Age (Mean)	Sex (F%)	MMSE (Mean) Dep/ Non-dep PDC
Vilalta-Franch et al. 2006 ^w	Spain/ Memory clinic	491	27.4	13.4	4.9	CAMDEX: 9.8 NPI-depression: 43.7	75.2	70.9	17.4/17
Teng et al. 2008 ^{*w}	United States of America/ AD Research centers	101	44	14	NA	CSDD: 30 GDS: 33 NPI-Q-dysphoria: 50	77.5	55.8	21/21.2
Lage Barca et al. 2010 ^{**w}	Norway/ Hospitals & nursing home	112	53.6	34.8	47.3	NR	83	69.6	10/11.1
Engedal et al. 2011 [*]	Norway/ Hospitals & nursing home	112	53.6	34.8	47.3	NR	83	69.6	10/11.1
Chiu et al. 2012 [*]	Taiwan/ Dementia Clinic	302	29.8	9.3	17.5	NPI-Q-depression: 54 HAM-D10: 49.7 HAM-D17: 13.2	77	67.2	13/16.3

Note: CAMDEX: Cambridge Examination for Mental Disorder of the Elderly; CSDD: Cornell Scale for Depression in Dementia; DSM: Diagnostic and Statistical Manual; F: female; GDS: Geriatric Depression Scale; HAMD: Hamilton rating scale for Depression; ICD: International Diagnostic Criteria; MDD: Major Depressive Disorder; MMSE: Mini-Mental State examination; *NA: Not applicable; NPI: Neuropsychiatric Inventory; NR: Not Reported. Reports PDC symptoms endorsement; PDC: Provisional Diagnostic Criteria; **Duplicate data with Engedal et al 2011; ^w Studies reporting data for diagnostic agreement.

Data from the studies examining the validity of the PDC with AD samples have shown that depression prevalence is more than 2-fold higher compared with a diagnosis based on DSM-MDD or the ICD criteria in the same AD sample. For example, our analysis of these data showed that the chance of having someone diagnosed as depressed by PDC is over double the chance of having someone diagnosed as depressed by the DSM major depression [OR: 2.328; 95% Confidence Interval (CI): 1.545- 3.508; P-value=0.000; N=4].

Considering the random effect model, the omnibus event rate (ER) estimate for PDC was 0.377 (~38%) with a 95% CI ranging from 0.272 to 0.494. This ER was heterogeneous [Q-value: 33.988; P-value: 0.000; between study variability I^2 : 91.173%; N=4], and it was consistent with the value of the calculated median prevalence (36.9%). The near 100% overlap between the median and the estimated aggregate omnibus ER suggests that the heterogeneity in those studies may not be a significant factor to warrant further investigation.

The omnibus ER estimate for the DSM was 0.162 (~16%) with a 95% CI ranging from 0.088 to 0.277. The heterogeneity estimates for this ER were similar to those for the PDC [Q-value: 39.416; P-value: 0.000; I^2 : 92.389]. It is noteworthy that although the prevalence estimate and the median show twice the magnitude for the prevalence of depression by the PDC in contrast to DSM-MDD, the range of reported prevalence remains constant (~26%). A similar approach was undertaken to assess the prevalence of depression by the ICD based on 3 studies: the aggregate ER estimate was 0.177 (~18%) with a 95% CI ranging from 0.047 to 0.485 (see Figure 1).

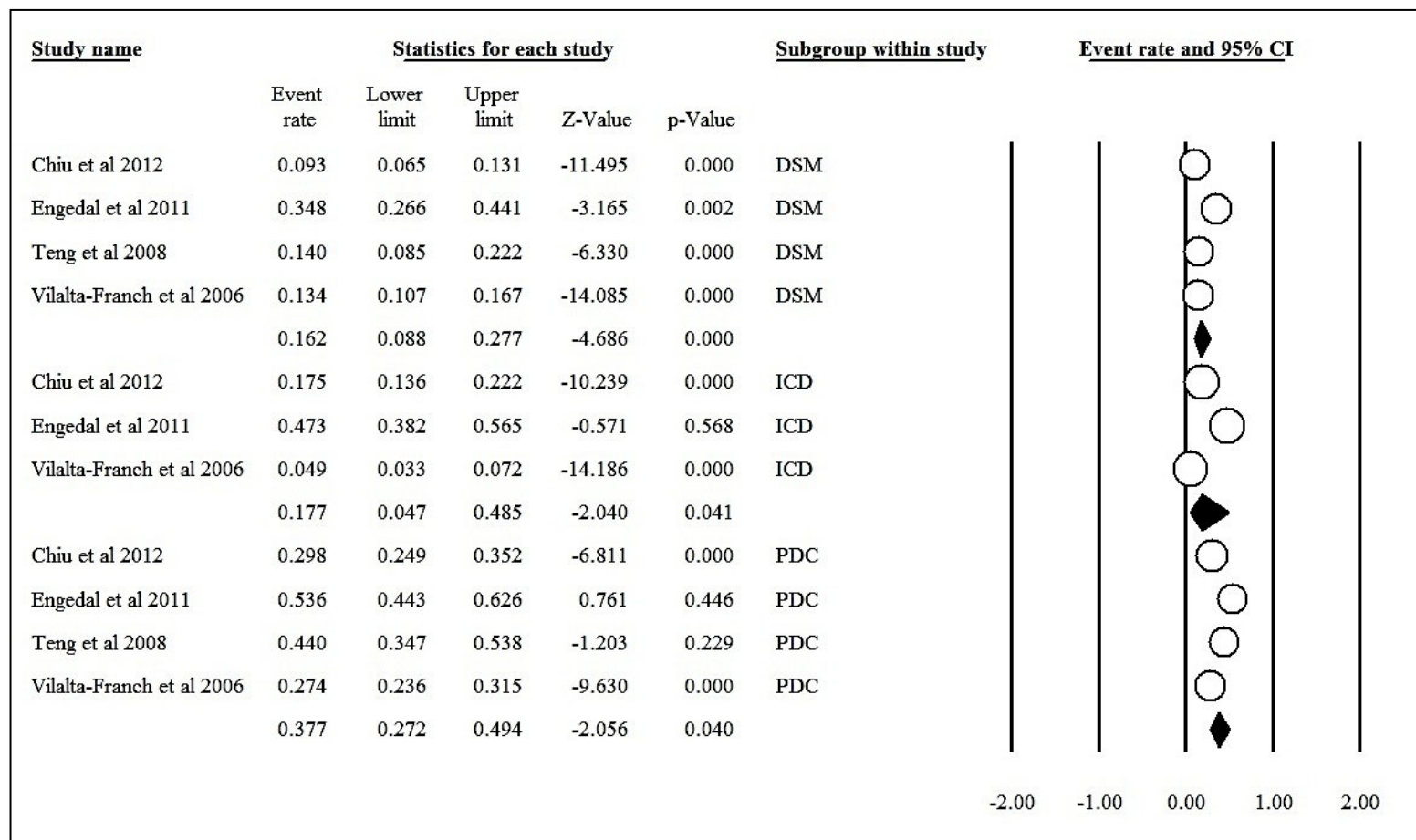


Figure 1. Forest-Plot (blobbogram) presenting the event rates

Note: The circles represent the individual event-rates, and the diamond is the aggregate event rate for each sub-group

Prevalence modifiers

Using the mixed effect regression model (method of moment) on the PDC data with age as covariate, showed that age significantly affected the meta-regression slope [Slope: 0.1456; SE: 0.079; P-value <0.001], suggesting that as the age increases the prevalence increases. The meta-regression with the mean MMSE scores for depressed as covariate showed an inverse relationship and was non-significant (Slope: -0.0290; SE: 0.0676; P-value: 0.0668). In this model, meta-regression of sex (percent overall female in each study) as covariate on Logit (log-odds) ER was non-significant [slope: -0.0230; SE: 0.0443; P-value: 0.6032]. The age was the single factor explaining 87.2% of the 91.171 % between study variability. Meta-regression of age, sex, and MMSE scores were not possible for the DSM data, given the lack of reported data in these collected studies. However, as per one study, there was no significant difference between DSM depressed and non-depressed on age and on MMSE scores.¹³⁴ These limitations render the comparison between the diagnostic criteria and sound interpretation of data difficult (see Figure 2).

Subsequently, quality assessment of the included studies was accomplished using the STROBE guideline for observational studies with a cross-sectional component.²⁵⁴ The quality rating of the included studies ranged from 58% to 80.6%; where the highest quality rating was associated with Teng et al 2008 and the lowest quality with Chiu et al 2012 studies. Further examination of the quality of studies on the prevalence (event rate) magnitude via mixed effect meta-regression model (method of moments) showed that as the quality rating increases, the Logit event rate –in other words the prevalence, increases [slope: 0.043; SE: 0.018; P-value: 0.017].

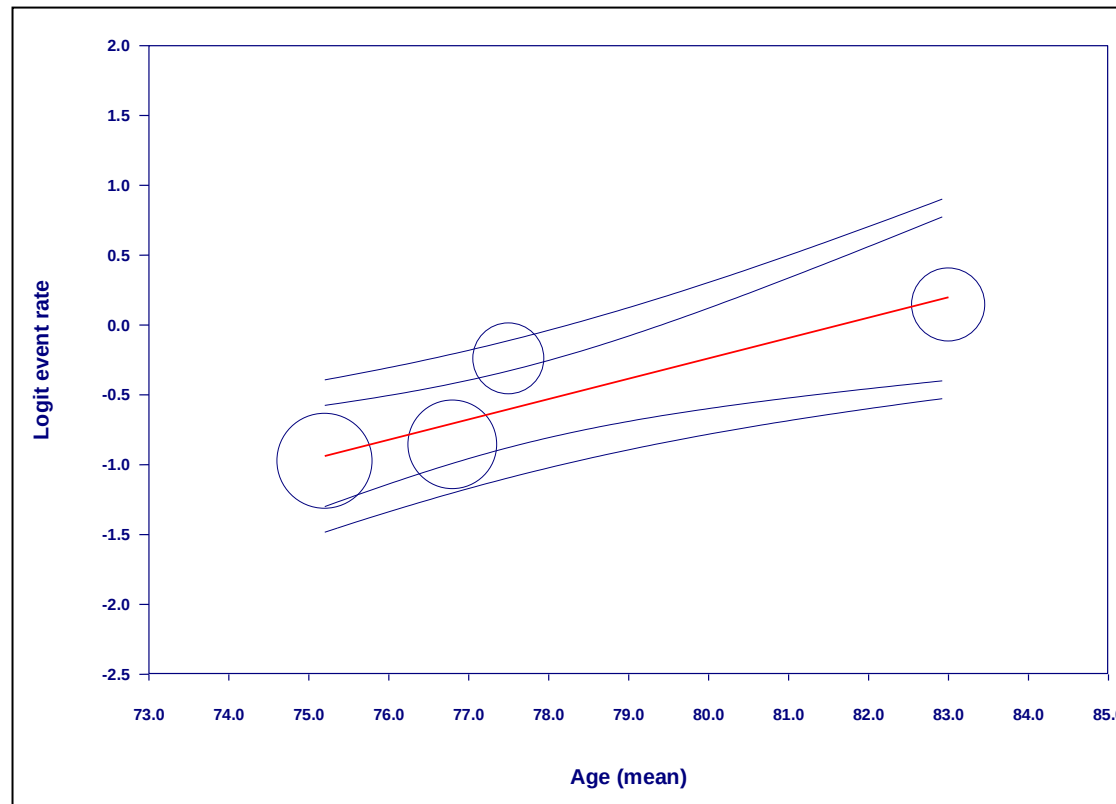


Figure 2. Scatterplot showing regression of Logit event rate for PDC on mean age (N=4).

Note: The size of each circle is proportional to the study's weight. Given the random effect model, the weight is equal to the total variance for each study. The middle line is the line of best fit, followed by the confidence and prediction line, respectively. Studies from lower age (mean) to higher age as a function of Logit event rate are: Vitalta , Chiu, Teng, and Barca/Engedal.

The funnel plot showed the presence of possible publication bias in the included studies; hence, we tried to overcome this limitation by using the Duval and Tweedie 'Trim and Fill' method.²⁶¹ By doing so, using the random effect model and the 95% CI, the effect size estimate remained the same 0.377 (CI: 0.272, 0.494), suggesting that the publication bias in this study is not an issue (see Figure 3).

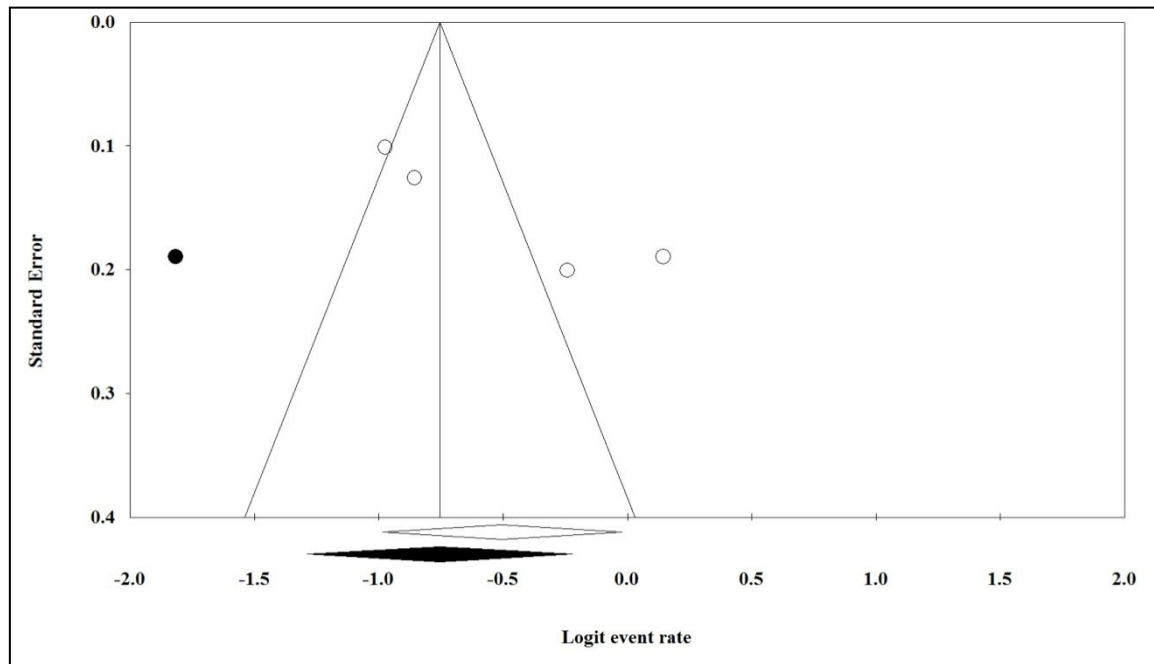


Figure 3. Funnel Plot of the standard error by Logit event rate for observed and imputed studies based on random effect model presenting publication bias in the included studies.

Note: Larger studies are positioned closer to the top. Missing study (hypothetical) is marked with bold filled circle. The middle line represents the mean and the other two lines represent the 95% confidence interval. In the absence of publication bias, the largest studies are plotted near the mean, and smaller studies spread evenly on both sides of the mean. Filled trapezoid represent adjusted point estimate suggesting a lower Logit event rate than the original estimate.

Diagnostic agreement

The diagnostic agreement between DSM and PDC varies considerably both at the individual¹⁴⁹ and at the group level.¹³⁴ Three studies (N=3) reported degree of overlap

between diagnostic criteria.^{134,152,260} In one sample, 43.6% of participants (61/140 cases) fulfilled both diagnosis of depression by PDC and DSM-MDD, 3.5% satisfied only DSM criteria, and 53% met PDC criteria alone.¹³⁴ A later study yielded similar results: 35% of subjects met PDC criteria alone whereas 65% met both PDC and DSM criteria.²⁶⁰ Another group reported that in their sample, 44% meet PDC criteria (44/101), 14% meet DSM-major depression and PDC (14/101), 22% meet DSM-minor depression and PDC (22/101), but only 8% of them meet PDC alone (8/101).¹⁵² In summary, consistent with the review and appendix by Geda and colleagues²⁶² the aggregate of the percent overlaps for MDD and PDC shows that the PDC are more inclusive than the DSM criteria in all studies (see Figure 4). However, regarding the validity of the PDC, when DSM minor depression is considered, the percent of patients meeting PDC alone is somewhat reduced, which in part supports not only the validity of the PDC, but also the fact that PDC seems to comprise a wider spectrum of symptoms, from very mild (or very unique) to minor depression to major depression.

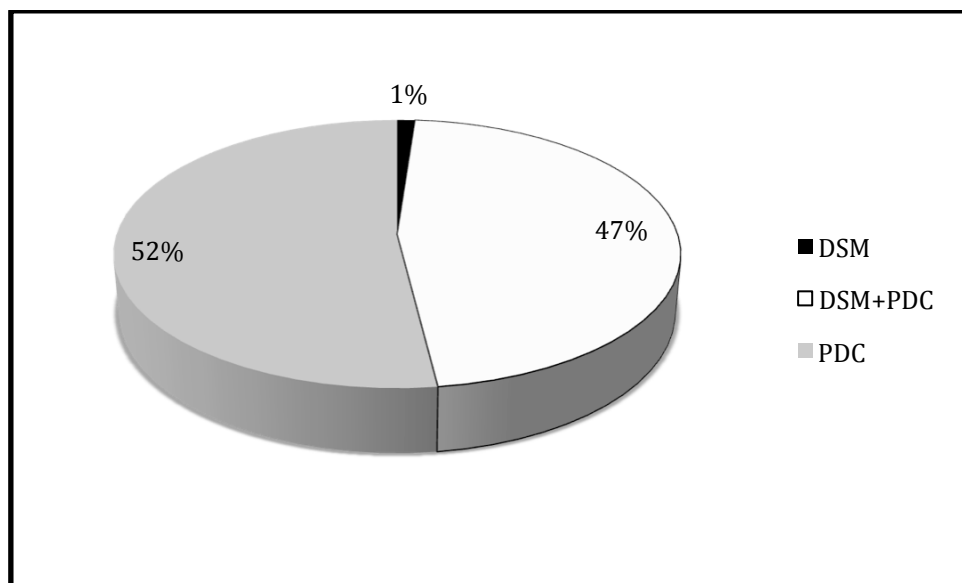


Figure 4. Aggregate percent overlap between PDC and DSM-MDD based on 3 studies^{134,152,260}

Symptoms presentation

Based on 3 studies reporting on the PDC symptoms,¹⁵²⁻¹⁵⁴ a total of 194 dAD patients provided endorsement for the 10 items on the PDC. After calculating the frequency of symptom endorsement from the pooled sample, “Depressed mood” and “Decreased positive affect or pleasure in response to social contacts and usual activities”, the two items of which either is required for diagnosis, were the most endorsed (78% and 67% respectively). The item “Fatigue or loss of energy” was third on the list with 63%; “Sleep disruption” ranked fourth with 62%. “Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt” and “Psychomotor changes” were at 59% and 56% respectively. Items novel to the PDC in contrast to the DSM, “Social isolation” and “Irritability”, were endorsed by nearly half of the patients with 51% and 45% respectively. “Suicidality” and “Appetite disruption” were the least endorsed items on the list with 34% and 32% respectively. In comparison to the PDC, the most prevalent symptoms by the DSM were “Depressed mood” (92%), “Decreased positive affect” (90%), and “Psychomotor changes” (82%), respectively. Consistent with the current literature, the PP for suicidal thoughts by the DSM (41%) was higher than the PDC. This may suggest the possibility of the PDC capturing an overall milder depression (see **Error! Reference source not found.**). The inclusion of irritability and social isolation items in the PDC and not the DSM-MDD does not necessarily mean that the DSM cases do not have these symptoms; they might have them but not recorded since the DSM does not require them.

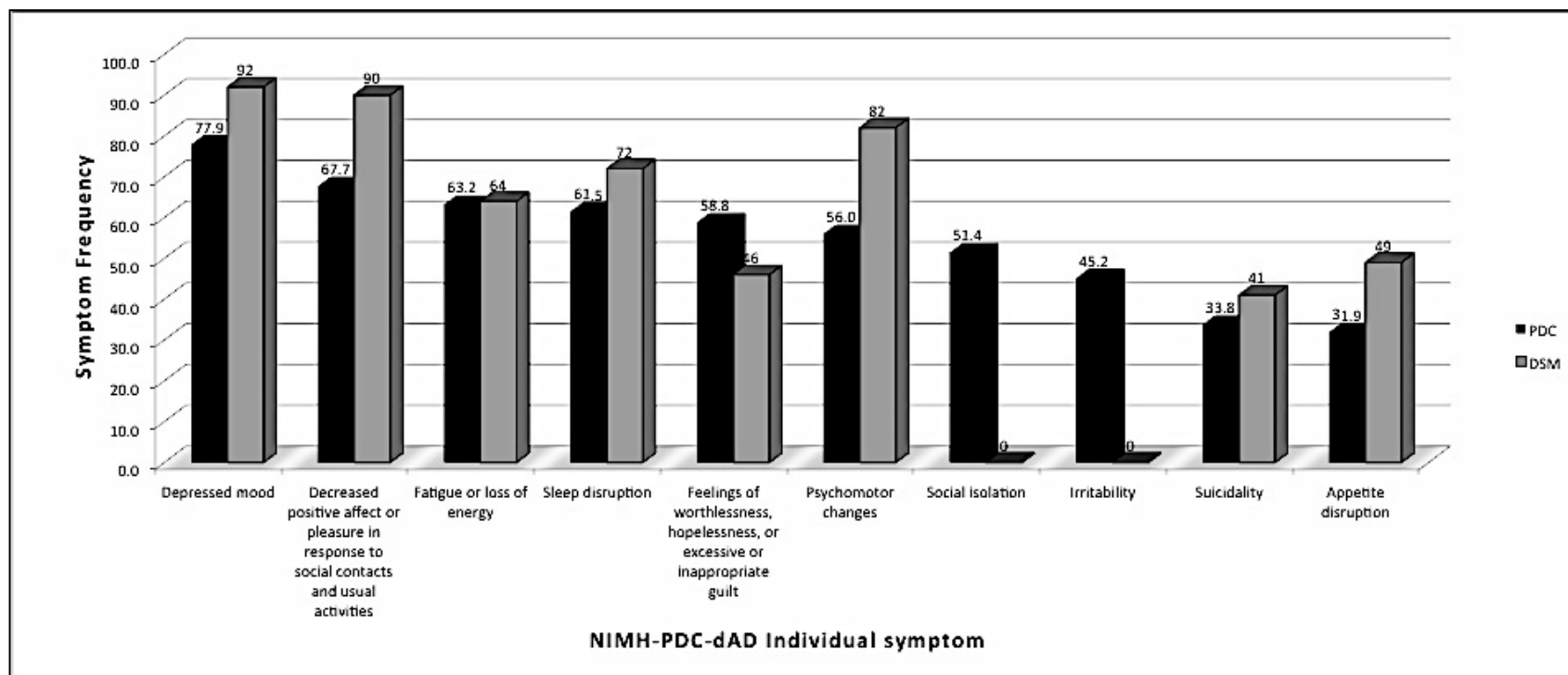


Figure 5. PDC symptoms endorsement from observational studies (N=3, n=194) and comparable DSM symptoms (N=1, n=39).¹⁵²⁻¹⁵⁴

Note the elevated feelings of worthlessness for PDC in contrast to DSM, in comparison to other symptoms.

Additionally, suicidal ideation and suicidal act are prima facie evidence of clinical depression. Therefore, we examined the available evidence for differences between DSM and PDC items or assessment scale items on suicidal ideation. For suicidal ideation, one dementia study showed comparable magnitude on suicidal thoughts, as measured by the Cornell Scale for Depression in Dementia (CSDD), between depressed and non-depressed subjects by DSM, ICD, or PDC, rated by nurses.¹⁵³ However, there were important differences in the percentage of subjects expressing suicidal ideation that met DSM criteria (31%), ICD criteria (23%) and finally PDC (20%). When a psychiatrist assessed patients, a lower frequency of suicidal thoughts was associated with the PDC (27%) than the DSM (41%) or ICD (28%). This specific evidence supports that the PDC, in aggregate, include milder forms of clinical depression, with overall the lowest rate of suicidal ideation among diagnostic criteria. It may be important to note here that non-demented normal older adults are less likely to verbalize suicidal thoughts and may experience death ideation, in the form of a passive wish to die. This would explain the overall lower point prevalence in comparison to other diagnostic items.³³ The finding of low rates of endorsement of suicidality by patients meeting the PDC may reflect lifespan changes in death ideation, or it may indicate depression experienced in parallel with diminished self-awareness and insight.

Differences between depressed and non-depressed patients

One study reported that subjects meeting the PDC showed a global Neuropsychiatric Inventory (NPI) mean rating score comparable to subjects diagnosed by the DSM [PDC: 13.1 (SD: 11.9); DSM: 14.3 (SD: 12); Cohen's d : 0.10]. Similarly, subjects not meeting either set of depression criteria scored comparably on the NPI [PDC no-depression: 9.4

(SD: 11.1); DSM no-depression: 8.9 (SD: 11); d : 0.04].¹³⁴ Only one study reported data on between group differences with DSM-IV major depression, and that showed no significant differences across all depressive symptoms on HAM-D > 10 or HAM-D score >17, and NPI (depression sub-scale).¹⁵⁴ This was a consistent trend with data reported on the DSM depressed versus non-depressed, where two of the included studies,^{134,152} without explicit narration of descriptive statistics, reported no significant differences between groups. In brief, no difference was found between DSM-MDD and PDC on the HAM-D and NPI.

In addition, two studies compared subjects meeting the PDC criteria (depressed) vs. subjects not meeting the criteria (non-depressed). Both report similarly large significant differences between these groups on the HAM-D and the CSDD (Cohen's d 1.32 and 1.12).^{153,154} There was no significant difference between the PDC depressed and non-depressed on the MMSE scores based on random effect model [Hedges' g : -0.121; $N=4$; 95% CI: -0.380 to 0.139; P-value: 0.363]. Consistent with omnibus results on depression, the effect size estimate for the MMSE was also heterogeneous [Q-value: 9.776; P-value: 0.021; I^2 : 69.313%].

In sum, current evidence from examining the differences between the PDC and DSM or PDC (depressed) versus PDC (non-depressed) supports the validity of the PDC. There was no significant difference between the PDC and DSM on the HAM-D, NPI, and NPI depression sub-scale, but there was a difference between PDC depressed and non-depressed on HAM-D and CSDD scores. However, the evidence is limited in that a reliable aggregate measure could only have been generated for the MMSE scores but not for the depression scales given the low number of studies.

Psychometric evidence

The NIMH panel of experts suggested the use of multiple scales with the PDC [e.g., the GDS, BDI, MADRS, and CSDD].⁸ To date, a decade later, such evidence comes from a limited number of studies with elderly patients of different nationalities with and without dementia-spectrum.^{155,260} For example, one study using the CSDD showed that the PDC is equally psychometrically accurate, in that the PDC showed on average 70% accuracy in comparison to 72% accuracy by the DSM and 71.5% by the ICD in a sample of 112 AD patients.²⁶⁰ Furthermore, at the lower cutoff score of 6/7 on the CSDD (meaning that a score of 7 and higher indicates a depressive disorder), the PDC showed substantially higher specificity (69%) than the DSM (60%) or ICD (66%). Similarly, the PDC was shown to have higher specificity (85%) at the higher cutoff score of 9/10 in comparison to the DSM (80%), and to the ICD (83%) with a sample of AD patients.²⁶⁰ In brief, these facts point to the strength of the PDC's validity.

In a study on mixed dementia patients, a lower cutoff score on the MADRS was needed to recognize dAD (9 versus 10, out of 60).¹⁵⁵ It is imperative to mention that MADRS is a sensitive measure designed to detect change in the treatment and severity of a depression episode as per the DSM criteria in general population.²⁶³ This study further reports the accuracy estimates of the scales, now validated for PDC: the MADRS at the cutoff score of 9 (lower cutoff score than for DSM or ICD) had a sensitivity of 74.7% and specificity of 75% for identifying dAD in 71 dementia patients; the CSDD, a dementia specific assessment scale as the name stipulates, at the best cutoff score of 11(lower cutoff score than for DSM or ICD), had a sensitivity of 80.4% and specificity of 66.7%; in other words, the accurate recognition of dAD in mixed dementia requires lower scores,

without a loss of accuracy: both scales showed overall higher Area Under the Curve (AUC) values for the PDC than for the DSM in a sample consisting of mixed-types of dementia and elderly outpatients.¹⁵⁵ In sum, it appears that depression scales in this study can detect dAD with high accuracy, though at a lower cutoff than for the DSM. The need for lower cutoff scores than for the DSM would indicate higher sensitivity resulting in fewer false negatives but raise concern with regards to false positives. Further investigations are required into what the appropriate severity threshold for a diagnosis of depression in AD is, and what the optimal approach is to screening depression in dementia – whether to query the patient, caregiver, or both.

In brief, to date only the MADRS and CSDD have been shown to have validity in the identification of dAD. There is no evidence that brief self- and/or informant-report scale(s) suited for screening for depression in AD populations can achieve similar accuracy.

Evidence from clinical trials

Current evidence includes few studies that utilized the PDC framework with AD, namely a) the first trial, an open-label investigation of the efficacy of escitalopram for dAD,²⁶⁴ b) a randomized controlled trial (RCT) examining the efficacy of sertraline on depression and cognition [i.e. Depression in Alzheimer's Disease-2 (DIADS-2)],²⁶⁵ and c) as a secondary outcome in a large mirtazapine and sertraline trial [i.e., Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD)].¹⁵⁰ Although there are challenges in comparing these trials, namely due to usage of different compounds and outcome measures (HAM-D and CSDD), the effect-size estimate has been non-significant with both diagnostic approaches when the best

available evidence was aggregated.²⁴⁰ Moreover, one study after examining for PDC symptoms in dementia severity-spectrum ranging from mild cognitive impairment to moderately severe dementia, further evaluated symptoms of patients treated with antidepressant (n=29) vs those not treated with antidepressant (n=49).²⁶⁶ There were a significant difference in terms of mean number of total endorsed symptoms, and only one symptom, decreased positive affect was significantly higher ($p=0.04$) for treated group (45 vs. 69%).

External validator

Two studies were found to provide added external validity to the PDC-dAD; these contributed neuropsychological and neuroimaging findings comparing depressed to non-depressed AD patients.

A Japanese team carried out the first neurocognitive comparative study of drug naïve (for antidepressant and cholinesterase inhibitor) probable AD patients diagnosed with PDC-dAD.²¹³ This study examined group differences via comprehensive neuropsychological assessment of 42 AD patients (including 21 dAD, over the period of 2 years). The groups were balanced for age, education, gender, and duration of dementia and depression. They have found no significant difference between PDC positive and PDC negative in terms of the scores on the WAIS-R, WMS-R (Logical memory I, Visual reproduction I) or the RAVLT. In contrast to the PDC negatives, the PDC positives took a longer time to complete the Trail Making Test (Part B) ($p < 0.001$), a sensitive test of cognitive flexibility and divided attention. Subsequently, a significant difference was observed between groups in terms of the score obtained by subtracting the time taken to complete the Trail Making Test (Part A) from that taken in the Trail Making Test (Part B)

($p < 0.001$). Furthermore, consistent with others, reported earlier, they found no significant difference between AD groups on global cognition as assessed by the MMSE. In conclusion, the authors stated that the PDC positives, but not PDC negatives, showed greater impairment of attention and executive functions, specifically pertaining to divided attention. Additionally, they suggested that although the PDC were used in their study, PDC remains to be validated for use with AD patients.

A team of researcher from Korea carried out the first neuroimaging study using the PDC as diagnostic criteria.²⁶⁷ This cross-sectional study used fluoro-deoxyglucose-Positron Emission Tomography (FDG-PET) neuroimaging approach to show brain metabolic differences between 24 drug naïve (for antidepressant) female PDC positives and PDC negatives AD patients. The groups were balanced for age, age of dementia onset, duration of dementia, education, and neurocognitive abilities, and consisted of very mild or patients with mild functional severity as assessed by clinical dementia rating scale. For assessment of cognition, they have used eight neuropsychological tasks including verbal fluency, 15-item Boston Naming test, MMSE, word list memory, word list recall, word list recognition, constructional praxis, and constructional recall, using the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet-Korean version (CERAD-K) battery. Generally, this study shows that the PDC positives had lower rate of metabolism in contrast to the negatives. Specifically, in contrast to the non-depressed AD patients, PDC positives had significant “hypometabolism in the right superior frontal gyrus (Brodmann’s area [BA], but regional metabolic reductions in the bilateral posterior cingulate (BA 31), left inferior temporal (BA 37), and right inferior

parietal cortex (BA 40)". In sum, they concluded that the frontal dysfunction is probably related to depressive syndrome.

The results of the two studies seem consistent in terms of neuropsychological funding and share the same limitation, that they have not compared PDC depressed to depressed by other diagnostic criteria, but have included a healthy normal patients, which limits the interpretation of them in light of PDC's external validity.

Discussion

This first qualitative examination of the 23 published works on the Provisional Diagnostic Criteria for depression of AD showed that: A) A higher prevalence of depression by PDC supports the framework's validity; dAD is assumed to be a different clinical entity, potentially including milder forms of depression, and the PDC were formulated to address the issue of under-recognition of depression in AD. B) The data on the diagnostic agreement between the PDC and DSM similarly support that the PDC is a broader entity, which may cover a wider spectrum of severity of depression in AD, thus resulting in a portion of patients only meeting these criteria. It is essential to note here that there are only a few cases of patients meeting DSM and not PDC criteria. These cases, were they more numerous, would constitute a problem in terms of validity. Also, it is important to note that although one of the PDC's exclusion criteria is that the symptoms are not better accounted for by other conditions, such as major depressive disorder, this is not an issue, when the PDC items are developed based upon DSM-MDD items. Thus, diagnostic overlap, when most items are similar, is expected. C) In terms of single symptoms, there is a similar pattern between the PDC and DSM. It appears that the new symptoms added to the PDC are useful in that mild-moderate AD patients endorse

them, or lack thereof in more severe dementia cases. D) Those meeting the PDC and those meeting the DSM do differ in terms of overall neuropsychiatric symptom burden, which shows that the PDC capture symptoms related to depression, not to other neuropsychiatric disturbances. E) The psychometric evidence suggests that the PDC require a lower cutoff point on well-established depression scales for dementia samples. At those cutoff points they capture dAD with high accuracy. It remains to be seen whether the cases identified with the lower cutoff (false positives by DSM cutoff) truly suffer from depression. In sum, the current validity study of the PDC, in line with what was suggested in the literature as validity evidence,²⁵² has examined concurrent validators (including psychological tests), prevalence difference, delineations from other diagnostic criteria, response to treatment, and external validators.

Limitation of the PDC

There are concerns about the temporal specifications of the PDC,²⁶⁸ or in psychometric terms, their reliability is not determined and needs refinement. Currently there is a lack of longitudinal studies to appraise this property of the PDC. In addition, optimizations of the PDC via subgrouping depression or refinements of the symptoms have been suggested. It is speculated that the PDC core criteria may not be suitable for AD patients of higher severity of cognitive impairment or they can be confounded with somatic complaints. For example, one study showed that PDC depressed patients with severe AD had lower indication of the sad mood.^{268,269} Of note, sad mood is only one of the two symptoms needed for diagnosis of depression, and this observation perhaps is sample dependent, such that self-awareness of emotional functioning in patients at a later stage of dementia is likely lower.²⁷⁰ On the other hand, one may question whether

patients with moderate to severe AD can actually experience sad mood. Or generally, is sad mood a core symptom of depression, or is a decreased positive affect (a symptom component of apathy) a sufficient and necessary core symptom? Nonetheless, the current review showed that depressed mood and decreased positive affect were the most commonly reported symptoms among those positively diagnosed with dAD.

It is possible that the PDC categorize four subtypes of depressive syndromes in dementia: reactive depression to cognitive impairment, recurrent depression, vascular comorbidities to AD causing depression, and AD progression leading to depressive symptoms.^{143,271} However, no study has tried to examine this quality of the PDC, and so it is suggested that further refinement of the PDC items is needed to better distinguish major depression, minor depression, dysthymia and adjustment disorder in AD,²⁷¹ that are heterogeneous factors in diagnosis of depression of AD.¹⁴³

Only one study²⁶⁶ examined the PDC in light of mixed dementia, and one used the PDC comparing mixed dementia to non-dementia in a validity study.¹⁵⁵ While there is a paucity of information regarding the utility of the PDC in other forms of dementia, in AD, the PDC have been used and explored in multiple published peer-reviewed and recognized professional journals, such as epidemiological papers, a case-series, and reviews.⁵⁷ Moreover, they have been commented on in a book chapter specific to depression in neurological conditions, which adds external validity. These facts are demonstrations of the level of acceptance of the criteria by the professional community at large.

Limitation of the study and current literature

The current work has certain limitations. For example, one of its limitations is in the studies included. Additionally, the fact that we have focused on comparing the PDC to DSM but not on the ICD in terms of symptoms can be a limitation, both in term of studying the PDC, and the scarcity of the literature on this argument. Furthermore, our search engines were the PubMed and EMBASE, which could be a limiting factor on its own accord. Nonetheless, it is highly doubtful that by expanding the list of search engines any further studies would have emerged given that the PubMed (Medline) and EMBASE are the most elaborate medical search engines to our knowledge. Furthermore, we omitted examination of depression as diagnosed by PDC in dementia spectrum, something that could have provided added external validity.

In terms of the current literature, there are limited available external validity criteria studies to allow further backing of the PDC. In fact, we acknowledge that there is a specific gap in the literature regarding external validators (i.e., family history, history of the syndrome, and course of the illness). Additionally, although some scales have been suggested and validated for use with the PDC, no short and easy to administer scale has been validated for screening of the PDC-dAD. Furthermore, we recognize the need for identifying among dAD patients those that would benefit from pharmacological and those that would benefit from non-pharmacological interventions using the PDC-dAD criteria. Besides, consistent with the goal of the International Society to Advance Alzheimer's Research and Treatment (ISTAART),²⁶² it is recognizable that there is a need for neurobiological studies of the PDC-dAD in order to facilitate treatment development and

implementation. Furthermore, the link between primary AD pathology and depression by the PDC also remains to be clarified.

To date, only pharmacological compounds (e.g., SSRIs) are used for treatment of depression by the PDC-dAD, and no non-pharmacological approaches to management of dAD are reported. New compounds should be investigated applying the PDC and also neurobiological studies using the PDC may point to new compounds. In addition, it is important to acknowledge that treatment response may vary as a function of depression severity,^{272,273} and that PDC-dAD severity needs to be determined to facilitate treatment selection. In line with previous work, even if predictors of these were known, different treatment approaches might need to be attempted before the optimum treatment is identified.²⁴¹

Moreover, in the current literature, there is no discussion of the quality of the evidence that substantiates the proposed PDC items. This limitation suggests the need for future examination of the evidence leading to refinement of specific PDC symptoms.

Conclusion

The finding that large portions of individuals meeting the PDC also meet DSM-MDD criteria means that there are similarities between the two diagnostic criteria. The finding that a large portion meets the PDC but not DSM criteria also has criterion validity because the PDC were developed to capture dAD, a more prevalent depressive entity^{134,152-154,260} distinct from DSM-MDD. However, important questions remain regarding individuals only meeting the PDC: are these individuals really depressed, and what evidence exists or will be needed to support this point? To answer the first question, evidence showed that once we combine minor depression to major depression criteria, the

degree of overlap changes, suggesting that a fraction of individuals remain that are only diagnosed by the PDC alone, and we cannot explain whether they are depressed or otherwise. From another standpoint, the psychometric data, the PDC+/DSM- people seem to suffer a softer depression given the non-significant differences for global cognition between depressed and non-depressed, overall symptom presentation as seen by the frequency of item endorsed, and lower rate of suicidal ideation.

The finding that age, but not gender or global cognition, was a factor influencing the prevalence of depression by the PDC criteria was an interesting observation. This observation needs to be compared to DSM or ICD data, which to date is lacking in the included studies. There is consistency with data from non-demented older adults general populations emanating from the CES-D that show, as we get older, the prevalence of depressive symptoms increases.¹⁹ It is important to suggest that, in dementia, older age means potentially being further along in the disease progression. In turn this would suggest that with progression of the disease, the number of patients with depression might increase. Although the evidence to date shows differently, and with greater variability in the trajectory of neuropsychiatric symptoms,²⁷⁴ it is likely that we see an increase in the prevalence of depression in dementia populations; however, it may not have been depicted given the cognitive impairment of these individuals.

Based on the available evidence, the PDC, although not the globally accepted standard, is the best standard that exists for identifying depression in AD. However, it would be desirable to have evidence of scores commonly used depression scales not examined to date and their cutoff for the PDC for further validation. Promising research avenues would be head-to-head examination of the PDC vs. DSM studies in AD where

criterion validity is examined concurrently via determination of quality of life and treatment response. Future studies should consider the type of AD diagnosis by incorporating biomarkers in the diagnostic frameworks. It is conceivable that depression of probable AD differs from depression in possible AD, given the potential mixed etiology in the latter entity, which may differentially impact depressive symptoms. It is also currently of considerable interest given the publication of new diagnostic criteria by the International Working Group (IWG) and by the National Institute on Aging (NIA) working group commissioned by the Alzheimer's Association (AA) (NIA-AA), that dAD evolves as a function of disease stage, from prodromal AD/MCI to full-blown dementia, and that a revision of the PDC will be required to accommodate the non-dementia stages of AD.^{58,275,276} By the same token, the emergence of the DSM-V diagnostic approach to cognitive impairment should be taken into consideration, given that the PDC relies on diagnosis of dementia by DSM. The DSM-V dementia criteria, major Neurocognitive Disorder (NCD) due to AD is specific to dementia and not to depression diagnosis co-existing with dementia. This new DSM criteria acknowledge depression symptoms, but not diagnosis of depression that co-exist in AD. The general descriptor for NCD can be behavioral (mood), but to the extent that it is not clinically significant. Moreover, the DSM specifier, Major NCD due to AD requires significant cognitive decline (2 or more cognitive domain), not due to other mental disorder, and that it interfere with persons' independence. Thus, we recognized that the PDC are needed to define depression as a disorder in AD (and not just a specifier), and to this end, a revision of the PDC is needed.

Chapter 4. Study 2 - The utility of depression scales for older adults in the detection of dAD by PDC

Synopsis

Background: It has been hypothesized that depression measures developed for older adults and validated for the Diagnostic and Statistical Manual of Mental Disorders (DSM) can detect depression of Alzheimer's disease (dAD) as defined by the 2002 Provisional Diagnostic Criteria (PDC). Our knowledge is limited on how depression-screening measures for older adults performs against the PDC. The PDC-dAD have been validated against interview-based depression scales for dementia, but not with short and easy to administer screening measures developed for older adults such as the Geriatric Depression Scale (GDS-30 based on self-report and GDSIF-30 based on informant collateral report) and Hubley Depression Scale for Older adults (HDS-OA). *Aim:* This observational study was carried out to A) examine and compare the utility of screening depression scales in the detection of depression of AD as defined by the NIMH-PDC (concurrent validity); and B) determine the construct validity (convergent and discriminant). *Method:* Subjects with AD and their informants were recruited from the UBCH-CARD, and completed select depression screening scales (GDS-30, GDSIF-30, and HDS-OA), Neuropsychiatric Inventory (NPI), Quality of Life in AD (QOL-AD), and Montreal Cognitive Assessment (MoCA). A clinician from UBCH-CARD assessed patients for dAD by the NIMH-PDC. Non-parametric statistical methods were selected to examine group differences, accuracy estimates, and correlations. For concurrent validity, Receiver Operating Characteristic Curve (ROC) analyses on the accuracy of depression

scores in detecting a dAD diagnosis was performed. For convergent validity, correlations between depression scales, NPI depression item scores and QOL-AD was computed. For discriminant validity, correlations between depression scales and MoCA scores were computed. *Results:* 39 dyads comprising of possible and probable AD patients with mild to moderate cognitive impairment (10 patients were PDC positive) were included. The PDC groups were significantly different on the 3 depression screening measures, where the PDC positives did poorly in contrast to the negatives. Depression scales showed high sensitivity, and moderate to high specificity for the PDC. The GDS-30 had the lowest specificity and a mediocre positive predictive value. The HDS-OA detected dAD as accurately as the GDS-30; the informant scale (GDSIF-30) detected dAD with higher accuracy than the patient rating scales. The construct (convergent and discriminant) validity of the depression scales was supported. As expected, the quality of life-AD inversely correlated with depression measures. *Conclusion:* The depression scales utilized in this study showed evidence of validity for use with the PDC. The informant rating scale showed higher psychometric properties in comparison to other depression screeners, thus it would be recommended for screening of depression of AD as defined by the PDC.

Aims

To provide evidence for the concurrent validity for dAD as defined by the PDC of depression screening measures for older adults:

1. Objectives related to the PDC

To determine and compare the overall accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of

each depression scale compared to the PDC (concurrent validity).

Subsequently, with optimal sensitivity and specificity, to derive cutoff scores that would allow classification of individuals into depressed and non-depressed (refer to Appendix A1 for the PDC-dAD).

2. Objectives related to the scales

- a. To investigate the subsets of construct validity, convergent and discriminant validity, of depression screening measures for older adults. For convergent validity (were two measures of the same construct correlate moderate to strongly with each other),^{277,278} depression scores will be correlated to one another (subject- vs. informant-based GDS (GDS-30 vs. GDSIF-30), subject-based GDS (GDS-30) vs. HDS-OA, and informant-based GDS (GDSIF-30) vs. HDS-OA), and to NPI sub-scale (depression/dysphoria) and QOL-AD scores. Also, to establish the discriminant validity (were two measures of differing construct do not correlation with each other),^{279,280} depression measures will be correlated with a global cognitive measure (e.g., MoCA).
- b. To establish the internal consistency reliability estimate, Cronbach's alpha will be computed for GDS-30, GDSIF-30, HDS-OA, NPI select sub-scales, and QOL-AD (see Appendix E to G for copy of the scales). Successively, the emerging data from the GDS-30 will be examined for the internal consistency reliability estimate of the shorter version of the GDS-30, the GDS-15.

- c. To investigate the relationship between presence of neuropsychiatric symptoms (burden) and the PDC diagnosis; and to provide further convergent validity-evidence by examining the relationship between the NPI depression subscale with the GDSIF-30 (correlation between two informant based scales). The NPI anxiety and apathy subscales will be explored given that they are common comorbidities with depression.

Background

The NIMH-Provisional Diagnostic Criteria for depression of Alzheimer's Disease (PDC-dAD) were proposed over a decade ago by a panel of experts. Based on broad sources of evidence and clinical observation the expert panel concluded that there is a depression specific to AD that is different from MDD.⁸ This panel was convened with several objectives in mind: A) To develop diagnostic criteria that potentially allows for homogeneity of symptoms, outcomes, and population under study; B) In response to garner a therapeutic claim from the FDA and to develop diagnostic criteria describing behavioral symptom clusters that are specific to depression in AD; C) To deal with the often recognized under-diagnosis of depression in AD,^{131,132} and allow better research and treatment implementation.

To date, only a few studies have examined the validity of the interview-based depression scales, including the Cornell Scale for Depression in Dementia (CSDD) and the Montgomery-Åsberg Depression Rating Scale (MADRS), for PDC-dAD. The validity of a brief and easy to administer self-report scale such as the GDS-30 with a parallel-version (GDSIF-30) for informants to provide collateral input for assessment of dAD, has not been examined. Presently the PDC are the best standard available for

diagnosis of depression in AD (as seen in Chapter 3), and appear more appropriate in light of the often-made claim of under-recognition and under-diagnosis^{131,141} of depression in AD made by the DSM criteria. Thus, the PDC are a better standard than the DSM for this study, which seeks to identify a valid and sensitive depression scale for screening of dAD. Hence, specifically, this study posits that, A) the Hubley Depression Rating Scale for Older Adults (HDS-OA), developed as an improvement over the Geriatric Depression Scale (GDS-30), can detect dAD by the PDC more accurately than the GDS-30. B) The Geriatric Depression Scale for Informants (GDSIF-30) and the patient version of the GDS-30 are equally accurate at detecting dAD; however, they may not be in full agreement with each other given that AD patients under-report while the informants over-report the symptoms. C) The responses from the patient and informant are both needed to determine dAD by the PDC. Consequently, a combination of the GDSIF-30 and GDS-30 scores will have higher accuracy than the HDS-OA. D) Quality of Life in AD score would be lower in those determined as dAD compared to those not meeting the PDC given the reported association between depression in dementia and quality of life^{281,282}; therefore, the QOL-AD measure is inversely correlated with the depression scales.

Methods

Design

A cross-sectional observational study was conducted to examine the utility of selected depression scales for mild and moderate AD severity as per the National Institutes of Aging-Alzheimer's Association (NIA-AA 2011 core clinical criteria)⁵⁸ (see Appendix B).

The GDS-30, GDSIF-30, HDS-OA, NPI, and QOL-AD were administered to all participants at a single time point. Participants were evaluated on PDC-dAD (Appendix A1 and A2) by their clinician at a single time point. Of note, clinician were not controlling for history of severe psychiatric diagnosis (e.g., bipolar disorder or schizophrenia). The depression scales (GDS-30 with a comparable informant version, GDSIF-30, and HDS-OA) were selected because they were easy to administer, short, and easily accessible. The GDS-30 was specifically selected because A) it has been validated for use with older adults with and without dementia; B) takes into account the somatic confounding factors affecting depression diagnosis in older adults;⁴⁵ C) it has a comparable informant version. The HDS-OA was selected specifically because it was developed to overcome the limitations of the GDS-30. The HDS-OA is based on the DSM-IV-MDD criteria, has reminders of the reference period, and is freely available.^{111,283,284} In combination, the HDS-OA and GDSIF-30 were providing convergent validity for the GDS-30. Scores obtained on global cognition via MoCA were used as a discriminant validity index. QOL-AD and NPI (the dysphoric item) scores were used as additional supports to convergent validity. Globally, the NPI total score was used for further examination of the validity of the depression scales, in addition to specifically providing neuropsychiatric context for dAD.

Participants

Research participants were recruited from the tertiary care UBC Hospital-Clinic of Alzheimer Disease and Related Disorders (UBCH-CARD). All participants had a diagnosis of either probable or possible AD in the mild or moderate stage of their illness. The operational definition for AD was based on the 2011 core clinical criteria for

diagnosis of AD.⁵⁸ This includes primarily meeting criteria for dementia, and secondarily meeting the following criteria for AD: (A) Insidious onset; (B) Clear-cut history of worsening of cognition by report or observation; and (C) The initial and most prominent cognitive deficits must be evident on history and examination in one of the ensuing domains: a) amnesic presentation, particularly recall, in addition to evidence of cognitive dysfunction in at least one other cognitive domain, such as b) non-amnesic presentations (language presentation, visuo-spatial presentation, or executive dysfunction).⁵⁸ (see Appendix B). Clinician impression of functional ability was used to assess the functional ability of the patients. Of note, as per routine memory assessment at the UBCH-CARD, the Modified Mini-Mental State (3MS)²⁸⁵ and MMSE scores were available to UBCH-CARD clinicians.

Inclusion criteria

1) Meeting criteria for possible/probable mild and moderate AD; 2) Ability to communicate in English; 3) Has a knowledgeable informant (e.g., someone who sees the participant at least 3-4 times/week).

Exclusion criteria

1) Current alcohol or drug abuse; 2) recent (<12month) head injury; 3) presence of active delirium or psychosis; 4) a history of psychiatric disorder other than depression; 5) being enrolled in a clinical trial (pharmacological or non-pharmacological); 6) any medical condition that in the opinion of the clinician could induce behavioral or mood changes, e.g. acute infections, nutrient deficiencies. (Refer to Appendix C for the form used for screening participants).

Procedures

Prior to beginning recruitment of participants for this study, a copy of the articles providing information on the PDC-dAD⁹ and a formulated screening sheet (Appendix D) based on the PDC-dAD was provided to UBCH-CARD clinicians. Also, a discussion session for review prior to application was set for all participating clinicians to ensure consistency in PDC-dAD administration. Before starting the research activity, an ethics approval for the project was given by the UBC-Clinical Research Ethics Board (REB #: H11-01598).

Trained individuals (the author and a research coordinator/assistant (RA) from the UBC AD research unit) screened UBCH-CARD patients' charts for inclusion and exclusion criteria. Charts of those potentially meeting criteria were reviewed and subsequently flagged for UBCH-CARD clinicians. Clinicians then made a judgment as to whether these individuals were suitable for the study, determined their interest in participation, and referred them for a detailed explanation of the study's purposes and procedures. Informed consent forms were provided to interested patients and informants. Given the evidence supporting the validity of the PDC and as per routine approach at the CARD, clinicians used the PDC and based on information from the chart, new clinical interview with the patient and informant, made the diagnosis of depression. Of note, the clinician were not specifically examining for the unspecified symptoms (e.g., irritability) that was missed in Appendix A1. The diagnosis was masked until post-recruitment and after the author or the assistant completed the assessment. See Appendix D for patient enrollment and recruitment procedure flow diagrams. Inter and intra-rater agreement among clinician was not possible given their time constraint and availability.

Study visit

Eligible participants with signed informed consent were screened for socio-demographic information (age, gender, & education) and confirmation of AD diagnostic status. As per UBCH-CARD usual memory testing, the MMSE scores ranging from 10 to 23 were used, where between 18 and 23 is considered as mild AD, and 10 to 17 as moderate AD.²⁸⁶ When possible, after signing the consent form, participants were invited to stay and complete the required assessment scales and interviews. Otherwise, an alternative appointment time was arranged to visit them either at home or at the clinic. In order to minimize the order effect, the order by which the RA or investigator administered the tests to patient or caregiver was determined by random generated numbers, where the investigator and the RA alternated between who was interviewing whom, patients or caregivers. However, this was only applied for some of the research participants (14 out of 39 dyads had counterbalanced order), given the limitation in the availability of the assistant, and time limitations in terms of patients' compliance and level of interest. For the remaining 25 dyads, the order of testing was dependent on the immediate availability of the caregiver. The different orders of scale administration were set so that practice and time effects would be neutralized. Generally, the order of test administration remained constant. The depression self-rating scales were administered to the patient in a question and answer interview format; for QOL, questions were asked and the answer options were displayed for the patient to select the answer that best reflected their perception of a given QOL item. Informant scales were self-completed by informants. For the NPI, the informant was interviewed. Patient-reported measures were considered "blank" should patients be unable or unwilling to respond to more than two

items on the scale. Other pertinent information, socio-demographic information (e.g., language and education), and medication regimen was collected from the patient's clinical history and gathered via the Case Report Form (CRF), previously prepared. A UBCH-CARD neurologist or geriatrician, blinded to the results from the scales, performed the clinical interview using the PDC,⁹ for assessment of depression, and classified patients as dAD present or absent (the primary outcome), and ascertained absence of non-depressive psychiatric symptoms (e.g., delirium or psychosis). Psychiatrist assessment of depression, an ideal approach, was largely not feasible because of the limited access to these clinicians; however, we deemed it acceptable to rely on the clinic's neurologist and geriatrician for the diagnosis of depression by PDC, as this approach has been applied in other similar studies.¹⁵⁴ The investigator and research assistant were fully blind to the clinicians' rating on the first 35 PDC diagnoses. For the remaining four diagnoses, there was un-blinding to the investigator because of a need to monitor fulfillment of the targeted sample size in groups deemed depressed by the PDC. To corroborate dementia diagnosis, the clinicians had access to results from validated and sensitive global neurocognitive assessment measures, the MMSE and the modified MMSE (3MS), and reinforced when needed by the MoCA. The clinicians were blind to the scores from the depression scales, except in cases where immediate attention was required, for example when subjects volunteered their suicidal thoughts or achieved very high depression scores based on current DSM-based cutoff scores.

Scales

DEPRESSION: The Geriatric Depression Scale (GDS)¹¹⁰ is a well-validated 30-item self-report screening measure with an average sensitivity of 0.75 and specificity of 0.77

(in elderly inpatients and outpatients from studies included in a meta-analysis based on mixed diagnostic systems excluding PDC-dAD).²⁸⁷ It has good concurrent and convergent validity against other well-validated depression measures.²⁸⁸ It has a dichotomized response format in reference to how the interviewee has felt over the past week. The scale is widely used with specific populations such as elderly medical inpatients, nursing home residents, and dementia populations.²⁸⁹ It is short, has a comparable informant version and is readily available. The GDS was specifically developed for older adults and has been validated not by focusing on depression diagnostic criteria, but rather by symptom presentations. Additionally, the GDS, a forced-choice response format self-report screening scale was formulated upon rational criteria of researchers and clinicians involved in geriatric psychiatry and gerontology,²⁹⁰ using the RDC²⁹¹ for depression, predating the DSM-III. The self-report approach for collecting symptom information was chosen given that characteristics of depression are largely subjective, in other words depends on the patients report.²⁹² The RDC was specifically developed to address the unique characteristics of depression that emerges in geriatric population that is mixed with somatic symptoms from other physical illnesses present in this population.^{293,294} Instead, the GDS focuses on the worries of the person and how they are interpreted in light of their quality of life. Moreover, it accounts for the subjective cognitive and specifically memory complaints of the elderly individuals with depression. The GDS was established based on 100 items related to depression in the elderly, and subsequently its content, construct, and criterion validity were tested.^{45,295} Henceforth, from the universe of original 100 items, only 30 best items were retained to capture depression in the elderly. Studies to date have shown that the GDS has no

significant relationship with measures assessing cognitive functioning, in other words has discriminant validity, in other words does not correlate with measures that does not measure depression.^{296,297} Evidence emerging from factor analysis studies also shows that the GDS is unidimensional,^{298,299} that it has high inter-correlation between its items (>0.80) and they uniquely support one factor. In other words, all of its items correlate with depression of the geriatric population. It has shown to have an acceptable level (>80%) of sensitivity and specificity in dementia patients with depression.³⁰⁰ However, evidence shows mixed results, for example some suggested that when the GDS is used with elderly persons who have mild and moderate levels of cognitive impairment, the diagnostic accuracy of the scale is low (the sensitivity rate is 25% and the specificity rate is 75%).³⁰¹ Also, the GDS may not be useful with dementia patients who are unaware of their cognitive deficit, because those dementia patients who disavow memory loss also tend to deny depressive symptoms on the GDS.²⁹⁶ Nonetheless, majority of studies suggest that the GDS can be used with older adults with mild-moderate cognitive impairment.^{302,303} Its collateral version has been suggested to be a preferable type of screen. Higher score and cut-off point on collateral version has been consistently reported.²⁹³ Some authors suggest that higher cut-off score for GDS is more suitable for patients with cognitive impairment.³⁰⁴ For these reasons, the GDS was expected to perform accurately in my study.

The Geriatric Depression Scale for Informants-30-item (GDSIF-30) is a screening test for geriatric depression as seen by the knowledgeable informant. It has a yes/no format and is easy to administer. It has been validated against other geriatric depression scales, and deemed to have a reliable (internal consistency reliability, $\alpha = 0.86$), and

acceptable sensitivity (0.60) and specificity (0.67) based on DSM-validated cutoff score of >9, to support its use for clinical utility.³⁰⁵ The Hubley Depression Scale for Older Adults (HDS-OA) is a brief 16-item, DSM-based scale screening for major depression symptoms occurring during the past two weeks. It was developed to screen older adults using a dichotomous response format (yes/no).²⁸³ It is written in larger font size¹¹¹ in contrast to other screening measures. Although the scale is validated against both the long-form and the short-form of the GDS,²⁸⁴ it offers some novelty since it is formulated with reminders of the reference period (During the past two weeks, have you....). See Appendix E1 to E3 for copies of the depression scales.

In order to provide an added justification for why the depression scales were selected, items overlap between depression measures and the PDC were examined *a priori*. A table was generated for depression measures versus the PDC-dAD, where PDC symptoms were on the horizontal axis, and the depression scale items on the vertical axis (see item comparison in Appendix K and L).

NEUROPSYCHIATRY: The Neuropsychiatric Inventory (NPI) is a caregiver interview assessing usually 12 psychopathology areas [delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, nighttime behavioral disturbances, and appetite and eating abnormalities] in terms of presence, frequency, severity and distress to caregiver. The NPI has inter-rater reliability ranging from 93.6% to 100%, depending on the sub-domain.³⁰⁶ In non-North-American populations (Dutch,³⁰⁷ Farsi,³⁰⁸ Icelandic³⁰⁹), it has shown acceptable convergent validity with the GDS-15 and GDS-30. However, there exist no North-American convergent validity data in comparison to the

GDS. (See Appendix F for a copy of the NPI-12 item). The NPI was administered to the informant. The total score for the NPI is the product of the frequency score (on a Likert-like scale: rarely to very often) multiplied by the severity score (on a Likert-like scale: mild to severe) of psychopathology presence in the patient. The sub-scales consist of multiple items tapping into the specific psychopathology: for depression 8 items, for anxiety 7 items, and for apathy 8 items are screening for the presence of symptoms. Higher scores on the NPI are suggestive of higher psychopathological concerns.

QUALITY OF LIFE: The Quality of Life scale for Alzheimer's Disease (QOL-AD) has 13 items and consists of 2 parts (see Appendix G for a copy of the QOL-AD). The scale collects information from both the patient (part 1) and the caregiver (part 2) on the patient's QOL on a Likert-like scale (from poor to excellent), with 1 being poor and 4 being excellent. Items were physical health, energy level, mood, living situation, memory, family, marriage, relationship with friends, self-estimate as a whole, ability to do chores and things for fun, money situation and life as a whole. A higher score signifies higher quality of life, where total scores for each part range from 13 to 52. The QOL-AD has good criterion and concurrent validity, excellent inter-rater reliability with Cohen's kappa value >0.70 , and a satisfactory internal consistency (Cronbach's alpha 0.82).³¹⁰ Noteworthy of mentioning that there is a substantial item overlap between the GDS's and the QOL-AD; however this is not a concern given the temporal order of the symptoms, as the GDS scales query about the past week and the QOL-AD about the current status.

COGNITION: The Montreal Cognitive Assessment (MoCA)²⁸⁶ is a rapid global cognitive screening measure amassing information from the patients on multiple cognitive functions including attention and concentration (e.g., digit span forward and

backward, and vigilance), executive functions (e.g., alternating trail-making), memory (e.g., delayed recall), language (e.g., sentence repetition, naming, and verbal fluency), visuoconstructional skills (e.g., cube and clock drawing), conceptual thinking (e.g., abstraction), calculations (e.g., serial 7), perception (e.g., naming), and orientation (e.g., time and space). Each task makes reference to multiple cognitive functions. Time needed to administer the MoCA is approximately 10 minutes. The total possible score is 30 points, where each item has a unique scoring method; a score of 26 or above is considered as normal. The MoCA is a valid and reliable scale for use in several languages and illnesses (e.g., frontotemporal dementia, mild cognitive impairment, and AD).³¹¹⁻³¹⁴ The scale is freely available online.

For the purpose of this study, MoCA was administered to provide information on the level of global cognitive performance.²⁸⁶ Additionally, the test was used to ascertain discriminant validity for depression scales. Specifically, the alternating trail-making part of the test was timed and for the first was used to differentiate the PDC depressed from the non-depressed given the fact that depressed individuals, as per the DSM criteria, are shown to have slower reaction time and mental processing speed.³¹⁵ See Appendix H for select psychometric properties of the scales used in this study.

Statistics

For data exploration and group differences: Scores from outcome measures were examined for shape of distribution, skewness, and homogeneity of variance using the kurtosis, skewness, and Levene's test, respectively. In the presence of abnormality in the shape or skewness, transformation of the data was undertaken using common standard methods (logarithm, square root, and multiplicative inverse). In the absence of normal

distribution, a decision was made to use non-parametric tests to compare groups (Mann-Whitney U, Chi-square, or Fisher's exact test), to examine correlations (Spearman's rho), and to assess the accuracy of the scales (empirical AUC analysis).

For objective 1: The Receiver Operating Characteristic Curve (ROC) was used as the primary statistic to assess the inherent utility of each scale with respect to the PDC-dAD. To establish concurrent criterion-related validity for dAD as per the PDC (as criterion variable= "gold standard"), Area Under the Curve (AUC), sensitivity, specificity, PPV and NPV were calculated for each depression measure.

The ROC curve shows the trade-off between sensitivity (S_n) on the Y-axis, and 1-specificity (S_p) [also called 1-the false positive, or presented by 100-specificity depending on the statistical package used] located on the X-axis. The aim was to detect as few false positives as possible. A good screening measure is one that has small false positive and false negative rates across a reasonable range of cutoff scores. Cutoff scores with the highest accuracy were determined for each scale, where the smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. However, determining the optimal cutoff scores was accomplished by visually assessing which score combines maximal sensitivity with optimal specificity (decision threshold).

Although arbitrary, a value for the AUC ranges from 0.50-0.75 (fair), 0.75-0.97 (good/very good), and 0.97-1.00 (100% as excellent). A good test is one with an ROC curve that rises to the upper left quadrant very quickly, showing better overall performance of the test. Current evidence shows that there is no significant difference between the empirical non-parametric and smoothed parametric AUC values;³¹⁶ however,

each method has its limitations.³¹⁷ One difference is observable at the presentation level, where the graph of the parametric method is smoothed, while the other is not. The empirical non-parametric curves along with the non-parametric standard error (DeLong et al. method)³¹⁸ are presented using the MedCalc software (trial version), when applicable [http://www.medcalc.org/literature_roc.php].

A composite score was computed by aggregating GDS-30 and GDSIF-30 scores to form the GDS-GDS. The composite score on the GDSs was equally subjected to ROC analysis.

For objective 2: To provide evidence for convergent and discriminant validity of the depression scales used with the PDC, where applicable, the non-parametric correlation coefficient (Spearman's rho) was calculated between different pairs of depression scales and between the patient-rating and the informant-rating scales. The relationship between the depression measures HDS-OA, GDS-30, and GDSIF-30 was to appraise the convergent validity; the correlation between depression scales and QOL-AD was to substantiate the evidence for convergent validity; and the correlation between the global cognitive measures (MoCA) was to inform on the discriminant validity of the depression scales. The relationship between the NPI (depression/dysphoria sub-scale) score and the depression measures was the reinforcing point for the convergent validity of the depression scales, particularly for the GDSIF-30, given that both scales were collecting collateral information about the patient. The correlation between the depression scales and other NPI subscales other than depression items was to add support for discriminant validity of the scales. The correlation of the composite GDSs score with the HDS-OA, NPI sub-scale and QOL-AD was investigated.

Current evidence shows that there is no guideline as to how low or how high a correlation magnitude in value has to be in order to confirm convergent/discriminant validity. However, it is suggested by experts that discriminant validity coefficient should be noticeably smaller in magnitude than the convergent validity coefficient.²⁸⁰

On a different note, Cohen³¹⁹ proposed the magnitude of correlation coefficient, where a correlation below 0.1 is considered as very weak, 0.1 to 0.3 as weak, 0.3 to 0.5 as moderate, and above 0.5 as strong/high. Thus, for convergent validity, the correlation between measures assessing the same construct should be in the range of 0.3 and higher, preferably over 0.5, and for discriminant validity, the correlation between measures with unrelated construct should be in the range of 0.3 and below. The higher the difference between the correlation magnitude for convergent and discriminant validity, the better it is, and thus it would be expected to have a high overall construct validity.

The presence of the neuropsychiatric symptoms (frequency x severity), in terms of group differences (PDC positives and PDC negatives) was examined.

To determine the possible constraint of reliability on the validity of the scales, the internal consistency reliability estimates (Cronbach's alpha) for the GDS-30, GDSIF-30, HDS-OA, NPI anxiety, apathy, and depression, and QOL-AD, in addition to the short version of the GDS-30, GDS-15 upon the obtained data were calculated. Additionally, in order to have support for utility of scales, the supportive evidence of validity is needed.

Overall, objective 1 and 2 should provide ample psychometric evidence to allow decision as to whether any of the select depression scales should be used as a screening measure for dAD, and subsequently allow better understanding of depression in AD.

Results

Descriptive statistics

Data collection started in late April 2013 and ended on November 29, 2013. From the pool of flagged possible participants, 41 were recruited. From these dyads, one dyad, after reviewing the consent form, declined to participate. An additional dyad, although having signed the consent forms and accepted to participate, later did not attend the subsequent visit given a change in their medical condition. In total, 39 dyads completed the research interviews. Overall, all patients answered all questions, and only one informant inadvertently missed answering one of the questions on the GDSIF-30. No circumstances emerged to require immediate attention by the clinician, so the blinding was not affected.

Of the 39 patients, 10 had a diagnosis of depression by the PDC acknowledged by the participating research physician (prevalence = 26%). Physicians participating in the research were practitioners in neurology, geriatric psychiatry, or geriatric medicine; they were informed on the rationale, background, and description of the PDC with key reference publications⁸⁻¹⁰ to administer the diagnosis of depression by the PDC. Examination of the clinical history of the depressed patients (n=10) showed that 1 had history of MDD as per psychiatric evaluation, and 3 others had history of depression and mood disorders as reported in geriatrician and neurologist evaluation. Eight of the depressed patients had PDC items B, C, D, and F confirmed (ticked positive by the clinician); and for the remaining, one had C, D, and F; and one had B, D, and F ticked (see appendix A1 for the list of items). For the non-depressed group (n=29), history of mild depression (1 case), emotional lability (1 case), emotional incontinence (1 case),

depression symptoms no diagnosis (3 cases), low mood no diagnosis (1 case), paranoia, hallucination, agitation, aggression, and anxiety were reported. For all others, psychiatric history was unremarkable. For the non-depressed, information on the item B, C, D, and F was not relevant for examination given that they did not meet criteria for depression; hence no further information is provided.

The median age of the patients was 73 (range: 52 to 89), and their median educational level was 15 (range: 7.5 to 25). Forty-four percent of the patients were female. For sample distribution in terms of diagnosis and AD severity see Table 3. English was the current spoken language, and a few of the participants were bilingual or multilingual, with additional languages including Chinese, Croat, Czech, French, German, and Portuguese. All of the patients had demonstrated functional ability adequate for their dementia stage as per clinician impression (data not shown). There was no significant difference between PDC+ and PDC- in term of AD diagnosis (Probable vs. Possible AD- Fisher's exact test: $P > 0.05$, 2-sided) or severity (Mild vs. others- Fisher's exact test: $P > 0.05$, 2-sided).

Table 3. Representation of the sample by AD diagnosis and severity by PDC groups

Category	Variable	Sample (n=39)	PDC+ (n=10)	PDC- (n=29)	P-value at alpha 0.05
Diagnosis	<i>Probable</i>	25 (64%)	7 (70%)	18 (62%)	NS
	<i>Possible</i>	14 (36%)	3 (30%)	11 (38%)	
Severity	<i>Mild</i>	25 (64%)	6 (60%)	19 (66%)	NS
	<i>Mild-Moderate</i>	7 (18%)	2 (20%)	5 (17%)	
	<i>Moderate</i>	5 (13%)	1 (10%)	4 (14%)	
	<i>Not-reported</i>	2 (5%)	1 (10%)	1 (3%)	

Note: NS= Non-significant; Non-parametric statistics were used to compare groups, for AD severity, groups were divided into mild and others.

For global cognition, the median MMSE score was 23 (range: 14 to 29). The highest scores of 28 and 29 for two patients were from the previous assessment, roughly a year prior to current assessment. The median 3MS score was 74 (range: 44 to 92). These scores were based on review of the charts, and thus the date of testing was not uniform with respect to the current study visit. The MoCA scores were collected at the time of clinician evaluation for dAD, or at most 2 weeks from the clinician evaluation. A similar time line was used with regards to the depression, neuropsychiatric, and quality of life scales administration. The median MoCA score was 16 (range: 6 to 25) (see Table 8 for distribution of scores by PDC diagnosis). The trail-making test part of the MoCA (timed) was collected for 37 out of 39 participating subjects. The two others did not complete the trail making time, given that their MoCA was completed at the clinic without timing this section, minutes before enrolling into the study. Currently there are no normative data for this component of the scale. The average score for MoCA in this sample was below the normative data for MCI (mean= 22; SD= 3.1), and consistent with the average reported for AD (mean= 16.2; SD= 4.8),²⁸⁶ suggesting that our sample consisted mostly of mild AD.

For depression, the median score for the GDS-30 was 7 (range: 0 to 21), for the GDSIF-30 was 12 (range: 2 to 29), and for the HDS-OA was 2 (range: 0 to 12). For psychopathology, the median NPI total score was 8 (range: 0 to 12), for depression was 1 (range: 0 to 8), for apathy was zero (range: 0 to 9); and for anxiety was zero (range: 0 to 12). For QOL, the median total score was 77 (range: 35 to 86), for the informant part was 35 (range: 21 to 43), and for the patient's self-report was 41 (range: 24 to 49). See Table 8 for distribution of the scores based on PDC diagnosis.

All of the patients were accompanied by knowledgeable informants, including daughters, sons, wives, husbands, common law partners, cousins, or friends. However there was no significant difference between PDC+ and PDC- when informant were categorized into spouses (including wife, husband, common law) versus children/others (including friend, cousin, son, daughter), (Pearson non-parametric Chi-square =0.002; degree of freedom= 1; P>0.05; 2-sided) (see Table 4 for details). The median age of the informant was 67 (range: 30 to 91). Thirty-three percent of the informants were male. The median education level of the informants was 16 (range: 12 to 24). In contrast to patients, the informants were more educated. There was no significant relationship between patient's age, education, and gender with the GDS-30 and HDS-OA, or informant's age, education, and gender with the GDSIF-30 (see Table 6).

Table 4. Relationship of participating informants to patients

<i>Categories</i>	<i>Informant</i>	<i>PDC</i>	<i>PDC+</i>	<i>PDC-</i>
Spouse	Wife	20 (51%)	6 (60%)	14 (48%)
	Husband	10 (26%)	2 (20%)	8 (28%)
	Common law	1 (3%)	-	1 (3%)
Children/ Others	Daughter	4 (10%)	1 (10%)	3 (10%)
	Son	2 (5%)	1 (10%)	1 (3%)
	Cousin	1 (3%)	-	1 (3%)
	Friend	1 (3%)	-	1 (3%)

Note: PDC= Provisional Diagnostic Criteria; +/-: positive and negative diagnosis; the percentage in the columns may not add-up to 100%, given the rounding of the number.

Normality of the sample with kurtosis (shape, “peakedness” of the distribution) and skewness (the degree to which a distribution of values deviates from symmetry around the mean) as well as the homogeneity of variance (Levene's test) was appraised for the GDS-30, GDSIF-30, and HDS-OA. The homogeneity of variance was met for the 3 scales (GDS-30: Levene's = 2.769, P-value= 0.105; GDSIF-30: Levene's = 1.372, P-

value= 0.249; HDS-OA: Levene's = 0.598, P-value=0.444). The assumption of normal distribution was not met for the HDS-OA and the GDSIF-30, where there was a low to acceptable moderate skewness in the GDS-30 and GDSIF-30 and high skewness in the HDS-OA. The kurtosis value for the global sample was negative and low for the GDS-30 and GDSIF-30 and moderately acceptable for the HDS-OA. Subsequent to global sample examination for normality of the distribution, within group examination of the skewness and kurtosis showed that there was a significant skewness and kurtosis for the PDC negative group for GDSIF-30 and PDC positive group for HDS-OA. Although the criteria are arbitrary, the cutoff score of 1 was set for both the skewness and kurtosis, where a value higher than this suggests asymmetry in the distribution of scores, or informs on the flatness/shape of the variable distribution, respectively.³²⁰

Data exploration was further performed on the NPI, MoCA, and the QOL-AD scores. The distribution of the scores based on kurtosis and skewness was not normal and was of concern when data was further divided by the depression diagnosis.

To correct for these distributional problems, before examining for group differences, square root data transformation approaches to the HDS-OA scores and Log transform using the absolute value of the reverse scores for the GDSIF-30 (given the negative skew) was carried out, but not for the GDS-30 scores (see Table 5). Transformation only changed the skewness and kurtosis results for the HDS-OA but not for the GDSIF-30, suggesting that the anomaly in the GDSIF-30 is due to one outlier rather than global variability in the score (see Figure 6 for distribution of data after square root transformation of the GDSIF-30 scores, and Table 5 for the results). Further investigation of the outlier at this point was halted because, A) by reducing the sample size we would

have affected our power, and affected the true results, B) more sophisticated statistical approach, such as model fitting and hypothesis testing were not intended, C) there were no obvious reasons, such as incorrectly entered or measured data, and D) there was no *a priori* set rule assigned as to what to do with an outlier if present. The limited change in the skewness and kurtosis suggested that the non-parametric statistics (e.g., Mann-Whitney U) must be applied on the raw scores to examine for within group differences and corrected for the number of outcome variables ($k=12$).

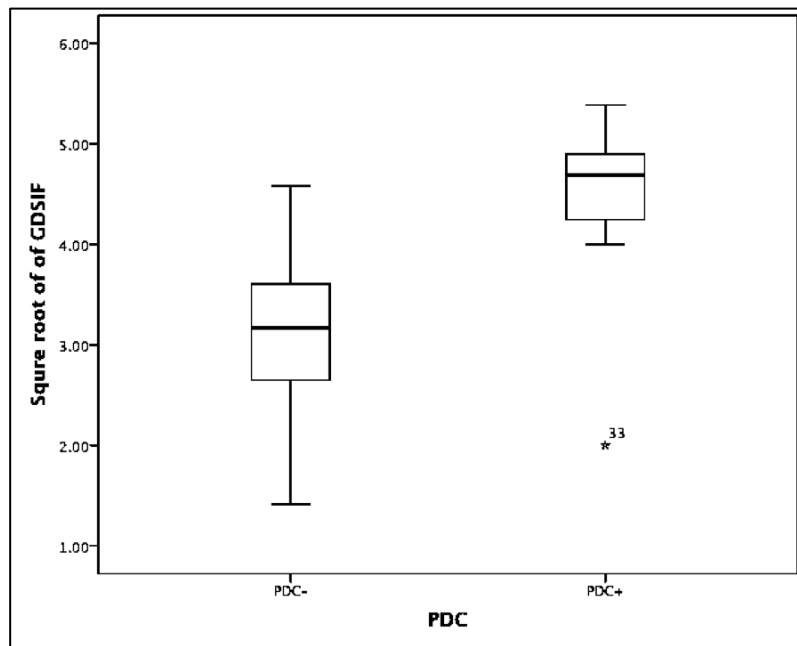


Figure 6. Box plot presenting the distribution of the data after using Square root transform for PDC- and PDC+, where PDC+ holds an outlier

Table 5. Distribution of the sample: Skewness and kurtosis before and after correction

<i>Depression scales</i>	<i>PDC dx</i>	<i>Skewness</i>	<i>Kurtosis</i>	<i>Corrected Skewness</i>	<i>Corrected Kurtosis</i>
GDS-30	Global	0.559	-0.629	-	-
	Positive	0.427	-1.168	-	-
	Negative	-0.646	-0.465	-	-
GDSIF-30	Global	0.522	-0.409	-	-
	Positive	-1.520	3.289	-2.135	5.489
	Negative	0.323	0.124	-0.392	0.458
HDS-OA	Global	1.231	1.202	-	-
	Positive	0.598	0.982	-0.311	0.391
	Negative	1.617	2.597	0.916	0.264

Note: Global n=39; Positive n=10; Negative n=29. Data transformation worsened the skewness and kurtosis for the GDSIF-30.

Table 6. Non-parametric Spearman's rho correlations between original depression scales and demographic variables

Variables	Statistics	GDS-30	HDS-OA	GDSIF-30
Age	Correlation coefficient	-0.102	-0.002	0.059
	Sig (2 tailed)	0.536	0.992	0.722
	N	39	39	39
Education	Correlation coefficient	-0.279	-0.180	-0.201
	Sig (2 tailed)	0.085	0.274	0.219
	N	39	39	39
Gender*	Correlation coefficient	0.233	0.168	-0.172
	Sig (2 tailed)	0.154	0.306	0.295
	N	39	39	39

Note: For GDSIF-30, age, education, and gender of the informant were taken. All correlations were non-significant at alpha 0.05. *For gender, female was coded as 0, male as 1.

In terms of the medication use for compounds related to dementia and depression, although different in terms of percentage, there were no statistical differences within groups (see Table 7).

Table 7. Medication regimen of the sample

	Antidepressant	Antipsychotic	Cholinesterase Inhibitor	Memantine
PDC- (n=29)	9 (31%)	2 (7%)	23 (79%)	2 (7%)
PDC+ (n=10)	6 (60%)	2 (20%)	9 (90%)	3 (30%)
Total sample (n=39)	15 (38%)	4 (10%)	32 (82%)	5 (13%)
Fisher's exact test	NS	NS	NS	NS

Note: PDC: Provisional Diagnostic Criteria (-/+). Numbers may not add up given that some patient were under multiple medications. Fisher's exact test was used given that we had 5 cases or less in at least one of the cells. Alpha level = 0.05. NS: Non-significant.

Antidepressants included: Citalopram, Desvenlafaxine, Escitalopram, Mirtazapine, Trazedone, Venlafaxine.

Antipsychotics included: Quetiapine and Risperdone.

Cholinesterase inhibitors included: Donepezil, Galantamine, Rivastigmine.

Given the non-normality of the sample distribution and remaining problems, a decision to resort to non-parametric statistics was made for the remainder of the analyses on the raw scores.

Group differences

There was no significant difference in depression diagnoses in terms of age, sex, and level of education of the patients, or age and education of the informant. However, a significant PDC group difference was observed on the 3 depression scales, GDS-30, GDSIF-30, and HDS-OA, as assessed by non-parametric statistical tests (Mann-Whitney U, alpha level = 0.004, corrected for the number of outcome measures). Tables 8 describe the sample in terms of diagnosis by the PDC.⁹

Also, there was no significant difference between groups with regards to *a priori* assessed global cognition via the MMSE (data not shown), and at time of testing with the MoCA. However, the PDC+ seemed cognitively slightly better than the PDC-, particularly so with regards to the global score as assessed by the MoCA.

Table 8. Representation of the patient sample in terms of PDC diagnosis

	<i>PDC+</i>					<i>PDC-</i>					MWU P-value
	n	Min	Max	Mean¶	Median	n	Min	Max	Mean¶	Median	
Patient Age (Years)	10	52	82	69.7	75	29	57	89	73.3	75	NS
Patient Education (Years)	10	11	20	14.6	16	29	7.5	25	14.9	14	NS
MoCA (Total)	9	9	25	17.3	16	29	6	25	15.3	16	NS
MoCA-Trail-Making (Sec)	9	11	59	28.4	35	28	9	87	47.5	45	NS
GDS-30	10	1	21	13.4	17	29	0	14	5.8	4	0.002*
GDSIF-30	10	4	29	20.3	21	29	2	21	10.6	10	0.001*
GDS-GDS	10	11	46	33.7	39	29	6	31	16.4	14	0.001*
HDS-OA	10	0	12	5	5	29	0	10	2.1	1	NS
NPI (Total-12 items)	10	1	62	23.8	26	29	0	28	8.6	7	NS
NPI (Depression)	10	0	8	3.4	2	29	0	6	0.9	0	NS
NPI (Apathy)	10	0	8	4	4	29	0	9	1.8	0	NS
NPI (Anxiety)	10	0	6	1.2	0	29	0	12	1.6	0	NS
QOL (Total)	10	45	79	61.4	70	29	57	86	78.2	77	NS
Informant Age (Years)	10	30	81	62.1	70	29	50	91	67.4	68	NS
Informant Education (Years)	10	13	18	15.5	16	29	12	24	16.0	16	NS

Note: GDS-30: Geriatric Depression Scale-30 items; GDSIF-30: Geriatric Depression Scale for Informants-30 Items; HDS-OA: Hubley Depression Scale for Older Adults; MoCA: Montreal Assessment Scale; NPI: Neuropsychiatric Inventory; QOL: Quality of Life-AD. GDS-GDS: the aggregate score for GDS-30 and GDSIF-30; MWU: Mann-Whitney U (MWU). NS: Non-significant.

*Significant at 0.004 alpha level given 12 outcome measures (corrected alpha 0.05/12). ¶: Here mean and median are reported, given that the difference between these measures of central tendency signals the degree of dispersion of the sample from the normal distribution. The larger the difference, the larger is the dispersion.

Overall, the PDC+ group showed a higher number of neuropsychiatric symptoms than the PDC-, but only by a few. Examination of the NPI items was carried out using the non-parametric independent Mann-Whitney U (MWU) test to examine within group differences (between PDC- and PDC+) based on the sum of scores. At alpha 0.004, there was a significant difference between PDC+ and PDC- on irritability (P-value = 0.003) but not for other items.

Reliability (internal consistency)

Internal consistency reliability of the depression scales was examined using the SPSS Cronbach's alpha in order to survey for the possible constraint of the reliability on validity of the scales. Given the relatively low sample size, a global (all items included) analysis has been carried out for the GDS-30, GDSIF-30, and HDS-OA, NPI subscales including depression, apathy and anxiety, and QOL-AD. Subsequently, based on the emerging GDS-30 data, similarly a reliability estimate for the GDS-15 was carried out. Items with zero variability were automatically excluded from each analysis. Here, although arbitrary, the cutoff score for determining quality of internal consistency was set to 0.70, where Cronbach's alpha (in this case, Kuder-Richardson 20, given the binary format of the data) value over this cut-off score is considered as an acceptable level of reliability index (see Table 9). The greater the Cronbach's alpha, the greater is the reliability index.

All measures with exception to NPI anxiety sub-scale, showed high level of reliability estimate, above the set cut-off score. Similarly, with exception to NPI anxiety subscale, there was very little discrepancy between the raw Cronbach's alpha (covariance between items) and Cronbach's alpha based on standardized items (correlation among items).³²¹

Table 9. SPSS reliability analysis [Cronbach's alpha (Binary KR₂₀)]

<i>Scales</i>	<i>Total Items</i>	<i>Cronbach's Alpha</i>	<i>Cronbach's Alpha Based on Standardized Items</i>
GDS-15*	15	0.815	0.821
GDS-30	30	0.891	0.889
GDSIF-30	30	0.887	0.883
HDS-OA	16	0.817	0.831
NPI (anxiety)**	7	0.619	0.565
NPI (apathy)	8	0.859	0.856
NPI (depression)**	7	0.802	0.815
QOL (informant)	13	0.825	0.834
QOL (patient)	13	0.854	0.848

Note: * Data from the observational study were used for this analysis.

**For the NPI (depression and anxiety) one item was removed due to zero variance in the results. Given the limited sample size in one of diagnostic groups (n=10), and the number of items included in the scales (majority included more than 10 items), no further analysis was carried out to examine for internal consistency as a function of diagnostic status.

Area under the curve (AUC)

Concurrent criterion-related validity of the depression scales was examined using the overall accuracy, sensitivity, specificity, and positive and negative predictive values (PPV and NPV) in differentiating PDC+ (depressed) and PDC- (non-depressed) patients. These values were obtained from the empirical non-parametric ROC analyses conducted using the DeLong et al. (1988) method³¹⁸ via the MedCalc software for Windows, trial version 12.5 (MedCalc Software, Ostend, Belgium). Here, the ROC analysis provides knowledge on the scales' ability to detect depression of AD. An AUC value of 0.70 to 0.80 is recognized as a fair diagnostic tool and anything higher than 0.90 to 1.00 as excellent.³²²

The empirical non-parametric AUC for the HDS-OA consisting of 16 items was 0.77 (SE: 0.09; P-value= 0.004) (see Table 10). A cutoff score of 2 out of 16 emerged for the

HDS-OA with the optimal balance between 80.0% sensitivity (20.0% false negatives) and 72.4% specificity (27.6% false positives). Here, given the high sensitivity of the PDC, greater emphasis was given to the specificity of the depression scale to determine the best cutoff score. With this cutoff score, the scale detects 50% of those that are truly depressed and 91.3% of those that are truly non-depressed as per the positive and negative predictive values, respectively.

For the GDS-30 (see Table 10), the AUC was 0.82 (SE: 0.09; P-value<0.001), and the best cutoff score was 8 out of 30, allowing for 80% sensitivity and 68.9% specificity. Similar positive (47.1%) and negative (90.9%) predictive values were observed for the GDS-30 in comparison to the HDS-OA.

For the GDSIF-30 (see Table 10), the AUC was higher at 0.88 (SE: 0.09; P-value<0.001). The best cutoff score was 17 out of 30 with sensitivity and specificity of 80.0% and 93.1%, respectively. The positive (80.0%) and the negative (93.1%) predictive values for the GDSIF-30 were substantially higher than for the patient self-report scales, the GDS-30 and the HDS-OA. For GDS-GDS, consisting of 60 items, the AUC was 0.88 (SE: 0.07; P-value<0.001). The optimal cutoff score was 24 out of 60 with sensitivity of 80% and specificity of 89.7%. For the positive and negative predictive values, the GDS-GDS was placed higher than both the patients' self-report scales, but lower than the informant scale, GDSIF-30. Figure 7 presents the empirical ROCs.

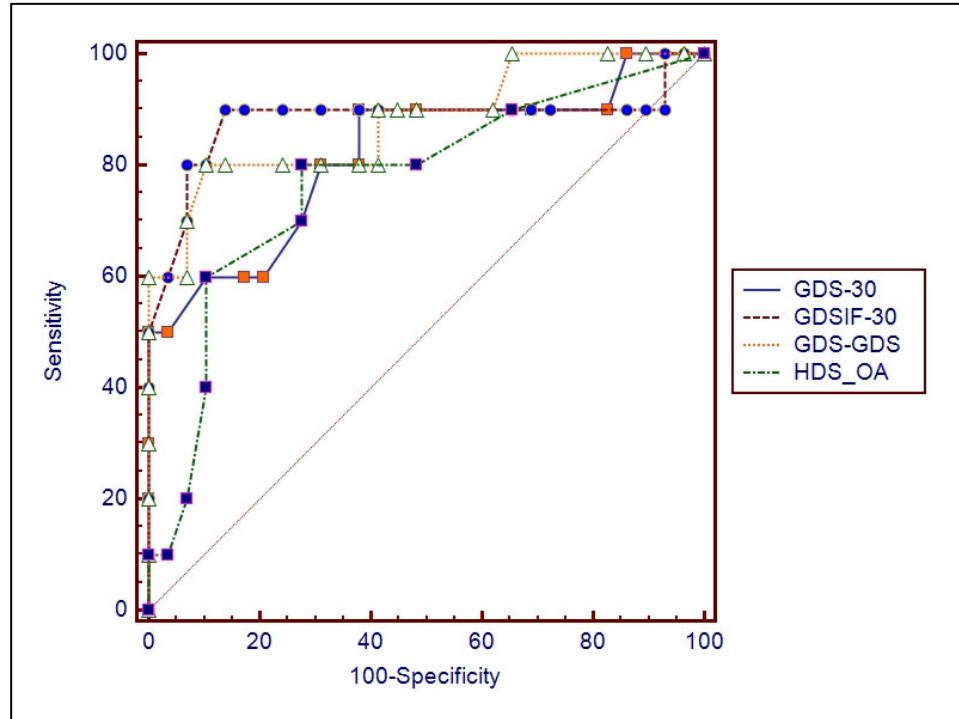


Figure 7. The empirical ROC curve for the depression scales: Sensitivity vs. False positive (1-Specificity). Overall, depression scales similarly performed better than by chance alone ($AUC > 0.5$).

Table 10. Area Under the Curve (AUC) and criterion values and coordinates

	AUC	SE (AUC)*	P-value	Cutoff	Se	Sp	+LR	+PV	-PV
HDS-OA	0.77	0.09	0.004	1	80	51.72	1.66	36.4	88.2
				2	80	72.41	2.90	50.0	91.3
				3	70	72.41	2.54	46.7	87.5
GDS-30	0.82	0.09	0.0005	7	80	62.07	2.11	42.1	90.0
				8	80	68.97	2.58	47.1	90.9
				9	70	72.41	2.54	46.7	87.5
GDSIF-30	0.88	0.09	0.0001	16	80	89.66	7.73	72.7	92.9
				17	80	93.10	11.60	80.0	93.1
				18	70	93.10	10.15	77.8	90.0
GDS-GDS	0.88	0.07	0.0001	17	80	58.62	1.93	40.0	89.5
				24	80	89.66	7.73	72.7	92.9
				29	70	93.10	10.15	77.8	90.0

Note: Alpha (<0.05); AUC =Area Under the Curve; CI = 95% Confidence Interval; HDS-OA = Hubley Depression Scale for Older Adults; GDS-30 = Geriatric Depression Scale – 30 items; GDSIF-30 = Geriatric Depression Scale for Informants – 30 Items; GDS-GDS = Aggregate from GDS-30 and GDSIF-30; +LR = Positive Likelihood Ratio; +PV = Positive Predictive Value; -PV = Negative Predictive Value; Se = Sensitivity; Sp = Specificity.*Based on the non-parametric DeLong et al. (1988) method. AUC values were the same when the Hanley and McNeil method³²³ was used.

Table 11. Diagnostic classification table between depression scales and PDC

<i>PDC Diagnosis</i>	GDS-30		GDSIF-30		HDS-OA	
	<i>Yes</i>	<i>No</i>	<i>Yes</i>	<i>No</i>	<i>Yes</i>	<i>No</i>
<i>Yes (positive)</i>	8	2	8	2	8	2
<i>No (negative)</i>	11	18	3	26	8	21

Note: GDS-30: Geriatric Depression Scale-30 items; GDSIF-30: Geriatric Depression Scale for Informants-30 Items; HDS-OA: Hubley Depression Scale for Older Adults; PDC: Provisional Diagnostic Criteria. The value in bold, represents the unexpected outcome, false positives.

Correlations (construct validity)

To investigate the construct (convergent/discriminant) validity of depression screening measures for older adults, the correlation between depression continuous scores and scores on scales not assessing depression was examined (see Table 12).

In terms of convergent validity, the Spearman's correlations for continuous scores between the HDS-OA and GDS-30, the HDS-OA and GDSIF-30, and the HDS-OA and GDS-GDS were moderate to large in magnitude ($\rho=0.732$, 0.415 , and 0.632 respectively). This shows a high level of convergent validity for the GDS-30, GDSIF-30 and HDS-OA. Moreover, the two different scales relying on self-report (GDS-30 and HDS-OA), and the two parallel scales relying on self- and informant-report (GDS-30 and GDSIF-30) show similar high correlations. The high convergent validity of the GDS-30 was marked by the correlation between the GDS-30 and scores of other depression measures (HDS-OA, GDSIF-30, and GDS-GDS). For the GDSIF-30, there was strong evidence for its convergent validity, through the strong correlation with patient-report depression scales (HDS-OA, and GDS-30) and even with the informant-based NPI

depression subscale ($\rho=0.626$). The aggregate GDS-GDS showed a strong convergent validity by the correlation between the GDS-GDS and depression measures (HDS-OA, GDS-30, and GDSIF-30). This relationship was strongest for the NPI depression subscale followed by the GDS-GDS aggregate, and weakest for the HDS-OA with this sample. All of the depression measures showed a weak to modest correlation to the NPI-depression sub-scale with the exception of the GDSIF-30 ($\rho=0.63$). Overall, as expected, a strong inverse statistical relationship between depression scores and the QOL-AD was observed.

To examine discriminant validity, the relationship between the depression scales and other scales not measuring depression, including the MoCA, and the NPI subscale for apathy and anxiety, were examined. No statistically significant correlations were observed between the HDS-OA and MoCA, and HDS-OA and the NPI-apathy ($\rho=0.1$ and -0.09 , respectively). Only an inverse modest relationship was observed between the HDS-OA and NPI-anxiety ($\rho= -0.30$). The weak correlations between the GDS-30 scores and the scores from MoCA, NPI-apathy, and NPI-anxiety ($\rho = -0.05, 0.04$, and -0.22 , respectively) were supporting evidence to discriminant validity of the GDS-30. For the GDSIF-30, there was strong evidence for its discriminant validity, through the correlation with scales not assessing depression (MoCA, NPI-apathy, NPI-anxiety). The GDS-GDS discriminant validity was also evident by the weak relationship between the GDS-GDS and the MoCA, NPI-anxiety, and NPI-apathy, respectively.

In addition, there was a significant and a strong relationship (Spearman's ρ) between the PDC and GDS, GDSIF-30, GDS-GDS, and NPI depression sub-scale, and a moderate to large magnitude relationship for HDS-OA. Table 13 summarizes the relationships.

Table 12. The Spearman's rho correlation matrix for the depression scales, subscales of NPI, Quality of Life, and MoCA.

	Statistics	HDS_OA	GDS-30	GDSIF-30	GDS-GDS	QOL (total)	NPI (depression)	NPI (anxiety)	NPI (apathy)	MoCA (total)
HDS_OA	Correlation Coefficient	1	.732**	.415**	.632**	-.398*	.335*	-0.295	-0.091	0.099
	Sig. (2-tailed)	.	0	0.009	0	0.012	0.037	0.068	0.58	0.553
GDS-30	Correlation Coefficient		1	.567**	.842**	-.497**	.361*	-0.222	0.039	-0.05
	Sig. (2-tailed)		.	0	0	0.001	0.024	0.175	0.814	0.767
GDSIF-30	Correlation Coefficient			1	.905**	-.628**	.626**	0.021	.345*	0.16
	Sig. (2-tailed)			.	0	0	0	0.901	0.032	0.336
GDS-GDS	Correlation Coefficient				1	-.597**	.572**	-0.088	0.225	0.092
	Sig. (2-tailed)				.	0	0	0.595	0.169	0.582
QOL (total)	Correlation Coefficient					1	-.484**	0.045	-0.159	0.041
	Sig. (2-tailed)					.	0.002	0.786	0.335	0.806
NPI (depression)	Correlation Coefficient						1	0.17	0.043	0.063
	Sig. (2-tailed)						.	0.301	0.797	0.707
NPI (anxiety)	Correlation Coefficient							1	0.103	0.054
	Sig. (2-tailed)							.	0.532	0.748
NPI (apathy)	Correlation Coefficient								1	0.252
	Sig. (2-tailed)								.	0.127
MoCA (total)	Correlation Coefficient									1
	Sig. (2-tailed)									.

Note: * Correlation is significant at the 0.05 alpha level (2-tailed). ** Correlation is significant at the 0.01 alpha level (2-tailed). The high correlation between the GDS-GDS and GDS-30 and GDSIF-30 is in part due to the fact that items from the GDS-GDS comprise items from the GDS-30 and GDSIF-30. With the exception of the MoCA (n=38), for all outcomes n=39 was used.

Table 13. Spearman’s rho correlation between the PDC and depression scales and global psychopathology

		<i>HDS_OA</i>	<i>GDS 30</i>	<i>GDS IF30</i>	<i>GDS GDS</i>	<i>NPI total</i>	<i>NPI depression</i>
PDC	Correlation Coefficient	.417**	.481**	.579**	.575**	.516**	.421**
	Sig. (2-tailed)	0.01	0.00	0.00	0.00	0.00	0.01
	N	39	39	39	39	39	39

Note: ** Correlation is significant at the 0.01 level (2-tailed); GDS-30: Geriatric Depression Scale-30 Items; GDSIF-30: Geriatric Depression Scale for Informant-30 Items; HDS-OA: Hubley Depression Scale for Older Adults; N: sample size; NPI: Neuropsychiatric Inventory; PDC: Provisional Diagnostic Criteria.

Discussion

The main objective of this study was to determine which depression scales have utility in detecting depression identified using the Provisional Diagnostic Criteria in AD (dAD). In terms of accuracy, the GDSIF-30 had a higher accuracy value than the GDS-30 at detecting dAD. In other words, in comparison to patient rating scales (GDS-30 and HDS-OA), the informant’ scale more accurately predicted detection of dAD, which is also evidenced by the relationship between the GDSIF-30 and the PDC, in comparison to the GDS-30 to the PDC or the HDS-OA to the PDC. The higher endorsement of individual items by informants in comparison to patients rating themselves was evident by the average and median scores for the GDSIF-30 in comparison to the average and median scores for the GDS-30, and the fact that the GDSIF-30 had a higher cutoff score compared to the GDS-30. There are a number of possible explanations for this outcome. For example, as suggested by others,³²⁴ one of the explanations could be the strength of the relationship between the caregiver and the patient (spouse/husband vs. friends or

children), or the affective state and cognition burden of the caregiver. Here we were unable to address these possibilities given that the cognitive and affective level of the caregiver was not assessed, and that we did not control for nor had the sample size to examine the strength of the relationship between caregiver and the patient.

The analysis of the internal consistency for the GDS-30, GDSIF-30, GDS-15, HDS-OA, NPI (depression, anxiety, and apathy), and QOL (informant and patient) was accomplished. With 7 items included in the analysis, the NPI anxiety had the lowest reliability index (Cronbach's alpha: 0.619), and with 30 items, the GDS-30 had the highest internal consistency reliability index (Cronbach's alpha: 0.89). In sum, the internal consistency analyses of the scales suggest that with exception to NPI anxiety, all scales including the GDS-30 may need modification to optimally function with the PDC. These may point to future content validity studies with a potential for the development of a new assessment scale or optimization of the existing one.

The GDS-30, GDSIF-30 and HDS-OA showed relatively high sensitivity of 80% when moderate to high specificity was taken into consideration. All of the depression scales had a satisfactory range of negative predictive value for all optimal cutoff scores (90.1 to 93.1%). However, the positive predictive value (PPV) was the determining factor, where the higher value belonged to the informant scale (GDSIF-30: 80%), and the lowest value to the self-report scales (GDS-30: 47.1%; HDS-OA: 50%). A PPV of 50% means that only half of those with a test result indicating depression have true depression. This is problematic given that positive scores on the scales are not particularly reliable. Furthermore, the informant- but not the patient-based scale, had a much higher specificity, suggesting that although all scales here showed an adequate diagnostic

ability, the informant scale outperformed the patient rating scales. These results raise three important points. First, these results are unexpected for the self-report scales, given that AD patients are expected to under-report. However, this can be interpreted in a different way, in that AD patients do not have a clear sense of their symptoms: they could report more symptoms at one time, or less at another. Nonetheless, the issue is more complex. Second, those that report depressive symptoms may in fact have depression but clinicians may have relied too much on the informant reports. Who is the ultimate judge of the patient's mood, quality of life, and affective well-being? While this is not an easy question to answer, it needs highlighting. Third, the clinicians were blinded to the rating scales scores in order to optimally diagnose patients with the PDC, thus the true positives/false negatives presented for each depression scale may not be as accurate as it should be. In the current study, patients were diagnosed as either with depression or not, and then assessed with the scales. Given the order of diagnosis and assessment, and ample psychometric evidence supporting the utility of the scales, I suggest that the scales can be used as screening tools. However, how the scales would perform in conjunction with a diagnostic interview, both applied by a clinician, needs to be determined.

The optimal cut-off score for the GDS-30 with the PDC was lower than the cutoff score for DSM major depression (8 versus 12). This trend was similar to the HDS-OA where the cutoff score based on the PDC was slightly lower than for the DSM major depression (2 versus 4).¹¹¹ The optimal cutoff score for the GDSIF-30 based on the PDC was lower than what is reported in the literature for DSM major depression (17 versus 21).³²⁴ The lower cutoff scores in comparison to the published DSM cutoff scores may suggest two things. First, in terms of the diagnostic criteria, dAD is indeed a milder form

of depression. Second, in terms of the scales, there are items in the scales that are not appropriate for the PDC, which indicates the need for a content validity study.

The construct validity evidence (convergent/discriminant) for the self-report scales was comparable. In terms of the convergent validity, the GDS-30 had a strong and significant relationship with the GDSIF-30. These suggest that the GDSs have an adequate convergent validity. A similar pattern was observed between the GDSIF-30 and the HDS-OA. The relationship between the GDS-GDS and the informant depression measure was equally strong and significant. It is worthy of mentioning that the high correlation between the GDS-GDS and GDS-30, and the GDS-GDS and GDSIF-30, is possibly because the GDS-GDS comprises items from the GDS-30 and GDSIF-30. As expected, the QOL-AD had a strong inverse correlation with the depression scales – GDS-30, HDS-OA, GDSIF-30, and GDS-GDS – which added value to convergent validity of the depression scales. The strong relationship between QOL-AD with GDS-30 and HDS-OA potentially can be criticized given the substantial item overlaps; nonetheless, given the different temporal presentation of the symptoms (current, past week, and past 2 weeks) among the scales, this issue may not be a concern. On the other hand, the medium to strong inverse relationship between the QOL-AD and depression scales is consistent with other studies, that quality of life is inversely related to depression.^{282,325}

With regards to the discriminant validity, the correlation between depression measures and the MoCA total score was weak to modest in magnitude. These suggest that the depression measures, including the GDS-30, GDSIF-30 and HDS-OA have adequate discriminant validity.

The current sample included 39 possible or probable AD patients, where 10 received a diagnosis of dAD (prevalence of 26%). This prevalence is higher than the 10% estimated based on the CARD chart data (see Appendix I). Additionally, the percent difference between these values is roughly consistent with the international data, appraised earlier (Chapter 3), where the prevalence of depression by the PDC was over double the prevalence of depression by the DSM criteria. There was no significant difference between PDC+ and PDC- on the global cognitive score. However, from the neuropsychiatric perspective, in this sample, there was a significant difference between patients diagnosed as depressed and those as non-depressed by the PDC, in that those with diagnosis of depression had higher prevalence of irritability symptom endorsement. However, future examination of the neuropsychiatric items, in terms of frequency and severity of symptoms for each PDC category, needs to be accomplished.

Clinicians should be cautious both in selecting which scale to use and in interpreting positive test results on the GDS-30 and HDS-OA, if they were selected, given that a decent negative predictive value but not positive predictive value was observed for these self-report measures, where only about half of those with a positive test have been diagnosed with dAD. From these data and the available evidence, given that the PDC is more inclusive (has a higher sensitivity) when used in conjunction with a scale with higher specificity and an acceptable level of sensitivity (e.g., GDSIF-30), one can speculate that clinicians could optimally identify patients that are truly suffering from depression. Therefore, by using these instruments with the specified cutoff scores, although, purely speculative, we possibly can lower the cost allocated to treatment of those that are wrongly diagnosed.

In brief, with regards to our hypotheses, whether the HDS-OA would outperform the GDS-30, the psychometric properties of the HDS-OA showed that it could detect dAD by PDC as accurately as the GDS-30, given the comparable AUC values. However, in terms of the AUC values, the GDS-30 scored higher than the HDS-OA. With regards to whether the GDSIF-30 would have equal accuracy and be in agreement with the GDS-30 for detecting the PDC, current evidence showed that the GDSIF-30 outperformed the GDS-30. With regards to whether both the GDS-30 and GDSIF-30 would be needed to determine dAD by the PDC, the current evidence showed that the aggregate measure, GDS-GDS, emanating from the sum of GDS-30 and GDSIF-30 scores, had a higher accuracy index in comparison to the GDS-30 and HDS-OA, but the same as the GDSIF-30. The fact that the GDS-GDS and GDSIF-30 had equal accuracy suggests that the patient information does not provide additional value to the GDS-GDS assessment scale. Given this fact, and that it would be challenging to get information from two sources, the development of an aggregate scale of the two GDSs would be perhaps futile for screening for dAD.

Limitations

This study has several limitations that originate around issues of validity, the choice of the scales, the study design, statistical power, and selection bias. Also, limitations that warrant replicating of the current study are the facts that the form provided to clinician for diagnosis of the PDC was missing an item; “irritability” (see Appendix A1 vs. Appendix A2), and that an interviewing guide,¹⁵² similar to SCID, was previously proposed for use with the PDC was not taken into account for the current study.

(a) Validity in terms of the PDC-dAD

1) The observational study used the PDC-dAD as a standard for diagnosis of depression, which currently represents the best available standard; however, it is considered provisional and is not fully accepted by most clinicians worldwide. All findings are based on the assumption that the PDC-dAD has construct validity as provided in Chapter 3. 2) Given that the participating clinicians have more familiarity with DSM-based symptoms, a potential concern is the bias of our clinicians in favor of the DSM in a study that did not use it. However, this limitation was partially overcome given that clinicians were provided with seminal papers on the PDC and *a priori* training-type session for review and discussion. 3) Another possible limitation of the study was the lack of parallel use of PDC with DSM criteria. This would have added direct comparability of the prevalence, and better understanding of not only the PDC, but also the assessment scales. 4) Given the lack of follow-up in this study, the cross-sectional observational study design was unfit to provide criterion-related validity evidence specific to the symptoms endorsement period of the PDC-dAD. This points to steps that should be taken in future longitudinal studies. For instance, with a longitudinal study design (or with a short follow-up), test-retest reliability of the scales as well as confirmation of diagnosis would potentially rule out the intra-individual mood variation as a possible confounding factor for the current results.

(b) Scales

The scales were designed prior to the PDC with different content, and thus this work contributes to better agreement of screening tools with the PDC. Furthermore, only a few

scales were included in this study for assessing depression, neuropsychiatric symptoms, and quality of life; this partly limits generalizability of the results. However, both self-report and informant-report markers of depression were included, which in turn facilitate better overall estimates of depression in AD. Additionally, given the low age range in our sample, selected scales for screening dAD may not be generalizable to adults between 45 to 65 years, given that they were validated for older adults; however, it is suggested that the GDS can be used and is validated for 17 years of age and older³²⁶. This project showed whether a patient- or informant-report scale was more useful for the PDC-dAD.

However, based on the internal consistency examination, provided earlier in this chapter, better scales with more refined items specific to the PDC or with added items surveying depression symptoms would be needed. As a result, content validity studies of depression measure are warranted.

(c) Generalizability of the results

Given the presentation of the sample, it is likely that these results hold true for mild to mildly moderate AD, but it cannot be generalizable to a more severe dementia nor to very mild cognitive impairment. I envision that the results may not be readily generalizable given that the sample consisted of both probable and possible AD, and that depression phenotype may be confounded by other co-existing neurological conditions such as vascular dementia, that was not controlled for. However, the results can be generalizable to primary care setting, particularly, in that depression screening measures could be used as a case-finding tool in contrast to psychiatric inpatient settings where case-finding is no longer an issue. Besides, the screening scales can be used for epidemiological studies as a method of case-seeking. By the same token, given that the PDC have been recommended

by others for use in nursing homes,³²⁷ and that nursing home staff detect depression less than psychiatrist as it was highlighted earlier; the use of these screening tools is warranted for such environment.

(d) Power

An initial limitation can be seen in terms of the sample size impacting the prevalence of depression as per the PDC. A lower prevalence rate than what is currently reported in the aggregate literature (26% vs. 38%) was observed (see Chapter 3). It is possible that the low sample size affected the specificity achieved in this study, which indirectly influences the obtained cut-off scores for depression scales. Additionally, given that the appraised aggregate prevalence of depression by the PDC was slightly more than double the prevalence of depression by DSM (roughly 38% versus 16%, see Chapter 3), and the appraised prevalence of depression in UBCH-CARD was roughly 10% (see Appendix I), it would be acceptable to assume that at CARD, the prevalence of depression by the PDC would be slightly more than 20%. By the same token, a sample consisting of 40 subjects from the CARD should contain roughly 8 patients with diagnosis of depression by the PDC. Thus, it was decided that 9 patients with depression would be sufficient and upon achieving this number, data collection was shortly ended. Similar studies reported samples ranging from 40 to 700.^{328,329}

Nonetheless, a reliable power was obtained (>80%) for the correlation coefficients using Cohen's criteria, and for the AUC analyses using the Hanley and McNeil criteria,³²³ a significant part of this work, suggesting that it is unlikely that a true difference or correlation was missed. However, of a lesser significance, the current sample may not have been sufficient for group comparison with multiple outcome

measure; thus a more stringent, Bonferroni correction was applied to appraise group differences and minimize chance findings.

(e) Selection bias

Selection bias in the current study may have played a significant role, particularly with regards to patient enrollment with a subsequent impact on the prevalence of depression by the PDC. Here, selection bias might have occurred on several occasions: initially when the clinicians were helping the project by recruiting more patients (PDC+ or PDC-), and subsequently, when the AD patients with more severe and higher number of symptoms would have declined from participating in this study. This last suggests that AD patients with more depressive symptoms may have opted not to enroll for the study. On the other hand, AD patients with lesser cognitive impairment were enrolled given a higher level of competence. Another possible confound to selection bias could have originated from the clinician's approach in corroborating information for diagnosis. For example, given the level of insight and cognitive impairment of the patient, and training of the clinicians, one may give more weight to the patient report of symptoms than to the informant. This may play in favor of enrolling patients with a milder level of dementia, as the more severe cases may be considered as unfit for participation in the study. To this end, we have failed to ask clinicians to what extent they rely on the informants versus the patients, something that needs to be done in future studies.

On a different note, it is imperative to highlight that the clinicians also had access to informants as collateral at interviewing time, and may have weighted their opinion higher than the patient in making the diagnosis, hence higher sensitivity/specificity was observed for the GDSIF-30.

Future directions

This study hints at promising further research directions. A few are highlighted as follows: A) Studies will be needed to relate our findings to AD severity. B) A longitudinal study with an added cross-sectional design would be desirable, in that the longitudinal component allows assessment of the reliability index (e.g., test-retest) for the scales, inter and intra-rater reliability of the diagnosis by clinicians, and examines the temporal resolution of the PDC, while the cross-sectional component of the study allows examination of the criterion-related evidence (e.g., DSM) for the PDC-dAD. C) Future applications may include development of definitive criteria for depression in dementia by examining the endorsement of individual PDC symptoms per AD severity; working depression phenotypes into diagnostic algorithms, particularly those helping in the differential diagnosis of AD vs. vascular disorders or mixed aetiologies; understanding the relationship of depression to brain dysfunction; and ultimately understanding depression on a continuum from psychological to biological causes. D) Given the low resources in terms of availability of clinicians at the UBC-CARD, inter and intra-rater reliability estimate were not assessed, something that needs assessment in future studies. Moreover, in the current study, the level of insight was not assessed, given that it was not the focus of the study and it was not hypothesized *a priori*. Nonetheless, this could have confounded our results or provided supporting diagnostic evidence. There is previous evidence to suggest that the discrepancy between patient rating of symptoms and informant providing collateral knowledge correlates inversely with depression.²¹⁷ Thus the knowledge of the magnitude of discrepancy would have endorsed the true positives and false negatives diagnoses. These warrant future studies examining the level of insight

in patients diagnosed by the PDC. In the end, recommendations and speculations to clinicians should be carried out with outmost caution till there are more studies on the validity of the PDC available.

Chapter 5. Study 3 - The content validity study of the Geriatric Depression Scale -30 (GDS) for the 2002 NIMH Provisional Diagnostic Criteria for depression of Alzheimer's disease (NIMH-PDC)

Synopsis

Background: Content validity is an important property of assessment scales used for establishing clinical judgments, especially when the trait is difficult to define. The use of subject matter experts (SME) for validation of the Geriatric Depression Scale-30 items (GDS-30) for content meeting the NIMH-Provisional Diagnostic Criteria for depression of Alzheimer's disease (PDC-dAD) has not been described to show whether the GDS-30 is optimal for the PDC and whether it needs optimization. *Objective:* To quantitatively and descriptively evaluate the content validity of the GDS-30 for depression of AD according to the NIMH-Provisional Diagnostic Criteria with feedback from experts.

Methods: Professionals with expertise in research or clinical work with depression in dementia were invited (n=26) to take part in a content validity study by completing a survey about the content of the GDS-30. The content validity index overall (CVI) and for each of the 30 items (I-CVIs) were calculated to inform decisions about whether to retain/reject or revise each item. Other test components are descriptively examined in order to assess the degree of their relevance and appropriateness for the target population.

Results: Six national and international SMEs agreed to judge the various components of the GDS-30 against the PDC-dAD. Expert ratings suggested that items pertaining to memory and cognitive functioning (GDS-30 items 4, 14, 23, and 30) be dropped. Only 8

items of the scale were fully endorsed to remain unchanged. The self-report approach to administer the scale to patients with mild cognitive impairment was fully endorsed; however, an administrator-read approach was suggested as more appropriate for patients with moderate to severe cognitive impairment. The dichotomized response format was judged to be appropriate for mild to moderate cognitive impairment but not for severe.

Conclusion: The GDS-30 was shown to have limited content validity for PDC-dAD. This study raised several questions, particularly with regards to the validity of the shorter version of the GDS-30, and whether to develop future scales fitting the PDC.

Aims

To examine content validity of the GDS-30 based on feedback from subject matter experts. The following aims will be undertaken:

- A) To examine the correspondence between GDS items and depression of AD as defined by the PDC.
- B) To examine of the degree of relevance of the elements of the GDS and their appropriateness for the target population.
- C) To examine the other shorter GDS versions (e.g., GDS-15) with current GDS-30 validity data (from chapter 4).
- D) To explore whether a new assessment scale is needed to capture the PDC optimally.
- E) To see how well the GDS assesses depression of AD

Background

Standardized scales of neuropsychiatric symptoms are popular for screening psychopathology in mental health research and clinical settings. The documented reliability and validity of such scales and the efficiency of administering them in research settings have led to their widespread adoption in studies of psychiatric and neurological problems. However, most scales in use today were developed during a period in which the constructs or domains they measure were undergoing revision.³³⁰ Specifically, a number of commonly used screening scales for the self-report of depressive symptoms were constructed prior to the inception of the NIMH-Provisional Diagnostic Criteria for depression of Alzheimer Disease (PDC-dAD).⁹ For example, the short and easily administered 30 item Geriatric Depression scale (GDS-30),¹⁰ albeit not designed in concert with the current Diagnostic and Statistical Manual for Mental Disorders (DSM),⁵ was developed prior to the development of the PDC. Thus, the GDS may not generally have content validity to be utilized as a screening measure for assessment of depression in clinical practice or research, or even specifically fit for a target population, even though it may have evidence of convergent and discriminant validity (see results from the concurrent observational study in Chapter 4). Nonetheless, the GDS-30 is widely administered for screening depression in older adults.

Content validity, a category of validity,³³¹ has been defined by many as “determination of the content representativeness or content relevance of the elements/items of an instrument”(Lynn, 1986, p. 382).³³²⁻³³⁴ Since Lynn’s work, the use of expert panels to evaluate the content validity of an instrument under development has become common practice.³³³ Recommendations are for expert panel members to be well versed, as a group,

in the topic,^{332,335} the conceptual framework underlying the instrument,³³⁵ and instrument development.^{336,337} As well, it is also important for members of the target population to be involved in the instrument content validation;³³⁵ nonetheless, this last must be approached with caution given the particularity of a participating patient population. For example, a concern was raised when the target SME group for evaluating a measure consisted of children or cognitively impaired adults. Again, a scale may be fit for an individual with a lower level of cognitive impairment but not for someone with substantial cognitive impairment as diagnosed by a physician. Content validation is an important psychometric property of an assessment scale, and for the GDS-30, the absence of this validity is an important caveat.

The GDS was designed specifically as a screening scale for rating depression in the elderly.⁴⁵ The GDS was not designed to follow the DSM. The authors of the measure suggested that it is more important to incorporate fewer somatic and more psychological symptoms of depression in the scale. They suggested that this approach would allow for greater ability to distinguish the non-depressed from the depressed in older adults prone to somatic symptoms due to aging, as well as having the ability to distinguish among severity levels of depression.⁴⁵

The PDC-dAD were proposed by the NIMH committee of experts over a decade ago to capture depression that is specific to AD (dAD).⁸⁻¹⁰ In brief, dAD requires the presence of three or more symptoms from a list of 10 and does not require the presence of symptoms for nearly every day, in contrast to the requirements of the DSM-Major Depression criteria.

There are multiple reasons for doing a content validity study. Generally, content validity is a good research practice for evaluating and documenting validity of assessment scales; strictly speaking, it is a standard for demonstrating validity. This is an important step for scale validation, and particularly for examination of the utility of the GDS as a screening measure for the PDC. As the content validity outcomes for the GDS do not appear to have been published, this study should show how well the GDS measures the behavior for which it is intended. Content validity allows us to make sense of the correspondence between GDS items and the symptom content of the syndrome, depression of AD as defined by the PDC. It would allow us to examine the degree of relevance of the elements of the GDS and their appropriateness for the target population. The content validation study here may serve initially as supporting evidence to the validity of the GDS as a screening measure for the PDC; also, given that the GDS is indirectly influenced by the Research Diagnostic Criteria (RDC) – partially related to the earlier versions of the DSM²⁹¹ – for depression,¹¹⁰ it further allows for construct validation of the PDC. In aggregate, content validity of the GDS would allow examination and potentially refinement of the assessment scale. Thus, the primary aim of this study is to examine the appropriateness of the 30-item Geriatric Depression Scale (GDS) as a screening measure for depression in AD using the NIMH-Provisional Diagnostic Criteria for depression of Alzheimer's disease (PDC-dAD) as the diagnostic standard.

Methods

Professionals with expertise in the subject matter, depression in dementia, were asked to complete a short survey in which they rate different aspects of the 30-item GDS in terms of the PDC-dAD and screening for depression in AD of various severity levels.

Initially, an invitation letter was prepared and sent to the individual experts. Upon acceptance to participate, a copy of the survey accompanied by the PDC symptoms was sent to each expert. The SMEs were selected based on their contribution to the development of the diagnostic criterion (i.e., the PDC), publication record and involvement in test/scale development specific for depression and dementia, or clinical work with this population.

The 6-page survey consisted of 11 questions (including multiple choice and open-ended questions) querying demographic information of the experts as well as the properties of the GDS-30. With regards to demographics, the survey gathered information on the age, gender, specialty, nature of work (practice/research/both), location of work (country/city), title, number of years in practice/research since graduation, and years of experience working with depression/with the elderly/with AD specifically. With regards to the assessment scale, the survey collected information on the appropriateness of the name of the scale, length of the assessment, instructions, approaches to collect information, the response format for the items, item relevance and content with the diagnostic criteria, appropriateness of the scale for a specific population of study, and test administration (see Appendix M for a copy of the survey). The survey was completed by one of our geriatric medicine clinicians as an example, and was estimated to take between 10 to 15 minutes for its completion.

For each question, responses were collected and tabulated for analyses. An agreement rating was generated for each question that had a dichotomized response format, and subsequently, the open-ended portion was examined. For those questions with a Likert-like response format, an agreement index was generated.

For the specific questions pertaining to the item relevance, the Content Validity Index (CVI) for the 30 items (I-CVIs) was calculated based on the agreement for inclusion (rating of 3 or 4, out of a maximum score of 4) or exclusion (rating of 1 or 2, out of a maximum of 4). Subsequently, an average of the I-CVIs was calculated in order to obtain an overall estimate of content validity for the GDS. This approach is different from the conventional definition of content validity: the proportion of experts who score items as relevant or representative only with either 3 or 4.³³⁵ The conventional approach tends to miss on some features. In the current study, it would miss: 1) the implication of the data emanating from the GDS-30 study on other GDSs (e.g., GDS-15); 2) the information from the rate of agreement (majority rating as 1 or 2) between the experts to either exclude or revise an item.

The CVI is a widely used approach to measure content validity, and to calculate for an instrument under development.^{332,338} It is suggested that an average agreement of 70% (0.70) is “necessary” for agreement, 80% (0.80) for “adequate agreement”, and 90% (0.90) for “good” agreement.^{339,340} Because the SMEs are expected to have extensive knowledge in the depression construct that is being measured, a low percentage of agreement in items should raise a red flag. Thus, it is suggested that a thorough examination of the pattern of scoring for each SME may help in identifying the reason for the low congruency.³⁴¹

Results

Demographics of the sample

Twenty-six national and international clinicians, researchers, or both, with expertise in dementia/aging and clinical depression, were invited via an email to take part in the content validity study. The invitation email was re-sent after a week to prompt the invited experts to reply to the request. Six out of 26 replied and accepted to take part in this study (23% acceptance rate, 2 had clinical experience using the PDC). The number of participants in this study is consistent of the typical number of SMEs (5 to 7) needed to examine a scale for content validity.^{333,341} The sample consisted of 4 males and 2 females. For those that reported their age (5 out of 6), the average age was 51 years [standard deviation (SD) = 6.75; range: 41-59]. With the exception of one expert (a neuropsychologist), others were physicians with a clinical specialty in neurology or geriatric psychiatry. Two out of the six had a PhD in addition to a clinical designation of MD. Four out of six experts were in both practice and research, and only two out of six were in practice only. The place of their practice was mainly in the United States (Los Angeles and Philadelphia) and Canada (London, Toronto, and Vancouver). On average, the experts had 21 years [SD = 8.18, range: 8 to 33] of experience in practice/research since graduation, 18 years [SD = 11.13, range: 1 to 30] working with depression, 18 years [SD = 9.25, range: 5 to 28] working with the elderly, and 18 years [SD = 9.25, range: 5 to 28] of experience working with AD patients (see Table 14). All SMEs provided full answers to the multiple choice and rating questions of the survey, and only a few did not provide full explanations to their answers.

Table 14. Demographic representation of the sample

Variables	SME-1	SME-2	SME-3	SME-4	SME-5	SME-6
Specialty	Geriatric Psychiatry	Neurology	Psychiatry	Neuropsychology	Geriatric Psychiatry	Neurology
Nature of work (In practice/research/both)	Both	Both	Both	Practice	Practice	Both
Location of work (country)	United States	United States	Canada	Canada	Canada	Canada
Title	Psychiatrist (MD)	Assistant professor (MD/PhD)	Professor (MD)	Neuropsychologist (PhD)	(MD/FRCPC)	Clinical Assistant professor (MD/FRCPC)
Number of years in practice/research since graduation	33	8	25	20	20	19
Years of experience working with depression	30	8	25	1	24	19
With elderly	28	8	25	5	21	19
With AD specifically	28	8	25	5	21	19

Note: NA= Not available; age and gender were not reported here, given that it would have allowed for identification of the experts.

Response to multiple-choice questions (quality assessment)

For Question 1, “Is the scale’s name appropriate for use with the PDC-dAD?”, 83% said yes, it is appropriate, and only 16% said that a different name would be more appropriate given the severity of cognitive impairment (see Table 15).

For Question 2, “If the GDS-30 were to be used for screening depression in AD, how would you describe the length of the assessment scale?”, 66% recommended that the scale was “too long”, and the remaining selected “about right”. Reasons for why it was too long were: that some of the items are irrelevant and they do not necessarily distinguish apathy from depression; that other versions of the test, the GDS-15 and GDS-10, are validated that could replace the 30-item test for screening; and that this increases the burden on patients.

For Question 3, “Is the instrument directive easy to understand for AD patients of different levels of cognitive impairment?”, 83% of the experts agreed that for mild cognitive impairment the scale was quite easy to very easy; 83% of the experts agreed that for moderate cognitive impairment the scale was somewhat to not at all easy; 100% of the experts agreed that for severe cognitive impairment, the scale was somewhat to not at all easy.

For Question 4, “How easy do you think the dichotomized response format of the GDS is for AD patients of different levels of cognitive impairment?”, 83% of the experts agreed that for mild cognitive impairment the response format was very easy; 66% of the experts agreed that for moderate cognitive impairment, the response format was quite easy to very easy; however, for severe cognitive impairment, the percent agreement was divided, in that 50% of the experts agreed that the response format was either not at all to

somewhat easy, and other 50% that suggested the response format was either quite easy to very easy. There was more heterogeneity in terms of responses in this sub-section of the survey, in that ranges of responses varied from 1 to 4.

For Question 5.1, “Is a self-report approach (in which the patient reads and responds to the GDS) appropriate for AD of different levels of cognitive impairment?”, 83% of the experts agreed that for mild cognitive impairment, the self-report approach is quite appropriate; 100% agreed that, for moderate and severe cognitive impairment, the self-report approach was somewhat to not at all appropriate, and particularly not at all appropriate for severe cognitive impairment.

For Question 5.2, “Is an administrator-read approach (in which an administrator reads the GDS items and records the patient’s answer) appropriate for AD of different levels of cognitive impairment?”, 66% agreed that for mild cognitive impairment this method of test administration was quite to very appropriate; similarly, this level of agreement was observed for moderate and severe cognitive impairment.

Table 15. Summary of the responses for questions 1 to 5

Questions	Responses	SME-1	SME-2	SME-3	SME-4	SME-5	SME-6	% Items rated 3 or 4	% Items rated 1 or 2	# of SME in Agreement
1-name	Yes	X	X	X	X		X	-	-	5
	No					X		-	-	1
2-length	Too Short							-	-	-
	About Right				X	X		-	-	2
	Too Long	X	X	X			X	-	-	4
3-directive	Mild cognitive impairment	3	3	4	3	2	4	.83	.17	5
	Moderate cognitive impairment	2	2	2	2	1	3	.17	.83	5
	Severe cognitive impairment	1	1	1	1	1	2	.00	1.00	6
4-easiness	Mild cognitive impairment	4	4	4	4	2	4	.83	.17	5
	Moderate cognitive impairment	3	4	4	4	2	2	.66	.33	4
	Severe cognitive impairment	3	2	3	4	2	1	.50	.50	3
5a-appropriateness for self-report	Mild cognitive impairment	3	3	3	2	3	3	.83	.17	5
	Moderate cognitive impairment	1	2	1	1	1	2	.00	1.00	6
	Severe cognitive impairment	1	1	1	1	1	1	.00	1.00	6
5b-appropriateness for administrator-read	Mild cognitive impairment	4	2	4	3	2	3	.66	.33	4
	Moderate cognitive impairment	4	2	4	3	1	3	.66	.33	4
	Severe cognitive impairment	4	3	4	4	1	1	.66	.33	4

Note: SME=Subject Matter Expert

Table 16. Summary of the responses for questions 7 to 11

Questions	Responses	SME-1	SME-2	SME-3	SME-4	SME-5	SME-6	% Items rated 3 or 4	% Items rated 1 or 2	# of SME in Agreement
7-symptom inclusion	Yes					X		-	-	1
	No	X	X	X	X		X	-	-	5
8-symptom needed	Yes	X	X	X			X	-	-	4
	No				X	X		-	-	2
9-symptom to remove	Yes	X	X	X			X	-	-	4
	No				X	X		-	-	2
10-open-endedness	Yes		X	X				-	-	2
	No	X			X	X	X	-	-	4
11-anything else	Yes					X	X	-	-	2
	No	X	X	X	X			-	-	4

Note: SME=Subject Matter Expert

For Question 10, “Do we need to add “please explain” for any GDS items?”, 66% (number in agreement = 4) of the expert respondents said that we should not add this to the items, given that dementia patients have a hard time with open-ended questions. The other 33% suggested that the probing statement could be added, specifically for item 27 (getting up in the morning), given that this item is not clear as to whether it addresses apathy or fatigue from sleep disruption. However, one expert particularly emphasized that all of the items may require additional explanations with moderate to severe AD (see Table 16).

For Question 11, “Is there anything else about the GDS that you would like to tell us when using it for screening depression in AD?”, 66% (number in agreement = 4) of the respondents said no, and the other 33% suggested that many of the cognitive symptom items are not relevant for depression in AD, and the screening should be done with the aid of an appropriate informant as well as the patient.

Response to multiple-choice questions (quantity assessment)

For Question 6, “To assign the level of relevance of the GDS items for the NIMH-PDC-dAD”, at the item level, given the *a priori* set 70% agreement cutoff score for inclusion/exclusion of an item, the following items were selected to be revised: items 4 (boredom), 14 (problem with memory), 23 (better off than others) and 30 (clearness of the mind), with 83% agreement between experts. Items 7 (good spirit), 9 (happiness), 10 (helplessness), 16 (downheartedness), 22 (hopelessness), 24 (upset), 25 (crying), and 27 (getting up in the morning) were items that had 83% agreement or higher to remain for screening of depression of AD. On four items, there was no clear agreement between experts whether to include or exclude them; these items were 1 (life satisfaction), 2

(dropping activities), 3 (life emptiness), and 19 (life excitement), and had 50% expert agreement to either exclude or include. The remaining 14 items had a 66% agreement to either include or exclude them. The average item-Content Validity Index was 0.74 (74%), which is slightly over the minimum average level required for validity, as suggested by several authors (see Table 1).

Table 16. Content validity index for GDS-30

GDS-items	S1	S2	S3	S4	S5	S6	# in agreement for responses of 1 or 2	# in agreement for responses of 3 or 4	I-CVI
1. Are you basically satisfied with your life?	2	2	3	4	2	4	3	3	.50
2. Have you dropped many of your activities and interests?	1	4	3	4	2	2	3	3	.50
3. Do you feel that your life is empty?	3	2	3	2	3	2	3	3	.50
4. Do you often get bored?	1	1	3	1	2	1	5	1	.83
5. Are you hopeful about the future?	2	3	4	1	4	3	2	4	.66
6. Are you bothered by thoughts you can't get out of your head?	1	3	2	3	2	1	4	2	.66
7. Are you in good spirits most of the time?	4	3	4	3	4	4	0	6	1.00
8. Are you afraid that something bad is going to happen to you?	1	3	3	1	3	3	2	4	.66
9. Do you feel happy most of the time?	4	3	4	4	4	4	0	6	1.00
10. Do you often feel helpless?	2	3	3	3	4	4	1	5	.83
11. Do you often get restless and fidgety?	2	4	3	3	3	2	2	4	.66
12. Do you prefer to stay at home rather than go out and do things?	1	4	3	1	2	2	4	2	.66
13. Do you frequently worry about the future?	2	3	3	2	4	3	2	4	.66
14. Do you feel you have more problems with memory than most?	1	1	2	4	2	1	5	1	.83
15. Do you think it is wonderful to be alive now?	4	2	4	1	3	3	2	4	.66
16. Do you feel downhearted and blue?	4	4	4	4	3	3	0	6	1.00
17. Do you feel pretty worthless the way you are now?	3	4	4	2	3	2	2	4	.66
18. Do you worry a lot about the past?	1	2	3	3	2	2	4	2	.66
19. Do you find life very exciting?	3	2	4	1	3	1	3	3	.50
20. Is it hard for you to get started on new projects?	1	4	3	2	2	2	4	2	.66
21. Do you feel full of energy?	2	4	4	2	3	3	2	4	.66
22. Do you feel that your situation is hopeless?	2	4	4	4	3	3	1	5	.83
23. Do you think that most people are better off than you are?	2	2	2	4	2	2	5	1	.83
24. Do you frequently get upset over little things?	3	4	3	4	3	2	1	5	.83
25. Do you frequently feel like crying?	4	4	4	4	3	4	0	6	1.00
26. Do you have trouble concentrating?	1	1	3	2	3	1	4	2	.66
27. Do you enjoy getting up in the morning?	4	3	4	3	3	3	0	6	1.00
28. Do you prefer to avoid social occasions?	2	4	4	1	2	2	4	2	.66
29. Is it easy for you to make decisions?	1	1	3	3	2	1	4	2	.66
30. Is your mind as clear as it used to be?	1	1	3	2	2	1	5	1	.83

Note: 1=not relevant; 2=somewhat relevant; 3=quite relevant; 4=highly relevant; CVI=content validity index; GDS-30=30-item Geriatric Depression scale. S=Subject matter expert, so S1 is SME#1. Items in bold refer to GDS-15. The I-CVIs in bold meet criteria for high number in agreement.

For question 7, “Have all of the PDC-dAD symptoms been included in the GDS?”, 83% of the SME agreed that several symptoms were missed, specifically items screening for suicidal thought, irritability, guilt, appetite, and sleep disruption.

For question 8, “Are there any additional symptoms or items that you think should be added for screening depression in AD?”, 66% agreed that more items are needed, such as items screening for irritability, appetite, suicidal thoughts, sleep disturbance, and anhedonia. The other 33% suggested that no further items are needed; however, without specifying the source, they suggested that collateral information is required.

For Question 9, “Are there any items that you think should be removed from the GDS-30?”, 66% of the respondents agreed that some items need to be removed, for example, item 14 concerning memory, and item 26 referring to concentration. Specifically, one expert also suggested that the item specific to boredom should be removed. Still others suggested that all of the items marked as irrelevant on question 6 should be removed. On the other hand, 33% of the respondents suggested that no change is required.

Post-hoc analysis

Given the responses from the SMEs, we conducted multiple ROC analyses using the data from the previous chapter, examining the AUC values with fewer numbers of items (see Table 17 for the results).

First the AUC was run for the shorter version of the GDS, GDS-15, that was suggested to be validated and recommended to be used by one of the SMEs (including items # 1, 2, 3, 4, 7, 8, 9, 10, 12, 14, 15, 17, 21, 22, and 23 of the GDS-30), then for the 8 items [including items # 7 (good spirit), 9 (happiness), 10 (helplessness), 16 (downheartedness), 22 (hopelessness), 24 (being upset), 25 (crying) and 27 (waking up in

the morning)) that had the highest CVI-I on the GDS-30, and subsequently, with all the items without the 4 items [including item # 4 (boredom), 14 (problem with memory), 23 (comparison to other people), and 30 (clear mind) of the GDS-30] suggested to be removed by the SMEs. All 3 proposed GDSs showed significant and high AUC values (threshold >0.5), comparable to the GDS-30 observed earlier, suggesting that by dropping items, there is little improvement in the GDS-30's AUC (see Table 17). Of note, the magnitude of the AUC values for the 3 GDSs is comparable to the Point-Biserial correlation coefficient (r_{pb}) of 0.515 to 0.562, where an r_{pb} value of 0.371 and over is considered a large effect.³⁴² However, when we examine the specificity of the scales, specificity increases as the number of items drop (e.g., from GDS-15 to GDS-8). Furthermore, a similar trend is observed in the negative predictive values. Additionally, the positive predictive values tend to decrease as the number of items increase (see Table 17).

The GDS-8 has the highest specificity and AUC value, with the lowest non-parametric standard error, compared to the other scales. This may be the optimal scale for use with the PDC to screen for depression. The fact that the GDS-30 or GDS-30-4 had the highest sensitivity is not surprising, given that higher numbers of items are correlated with higher possibility of screening patients as disease positive (and maybe more false positives).

Table 17. The representation of the empirical non-parametric ROC analyses results

<i>GDSs</i>	<i>AUC</i>	<i>SE</i>	<i>P-value</i>	<i>Cutoff*</i>	<i>Se</i>	<i>Sp</i>	<i>PPV</i>	<i>NPV</i>
GDS-30	0.82	0.09	0.005	8**	80	68.97	47.1	90.9
GDS-30-4	0.82	0.09	0.007	5	90	68.97	50.0	95.2
GDS-15	0.80	0.09	0.0015	5	60	86.21	60.0	86.2
GDS-8	0.83	0.08	0.0001	3	60	93.10	75.0	87.1

Note: * based on the Youden Index; ** based on experimental data from the observational study; PPV: Positive Predictive Value; NPV: Negative Predictive Value; Se: Sensitivity; Sp: Specificity. SE: Standard Error as estimated by the DeLong et al. method.³¹⁸

Discussion

This first content validity study of the GDS-30 for use with the PDC-dAD was accomplished with the aid of six national and international SMEs with several years of experience working with dementia and depression. Here, as suggested by experts that in order to make a sound interpretation of the validity studies of a measure,³⁴³ the concurrent interpretation of construct and content validity studies of the GDS-30 for PDC are presented hand in hand.

Germane to the utility of the GDS-30 for the NIMH-PDC-dAD, the majority of the experts agreed that the GDS-30 items were not inclusive of the symptoms of PDC-dAD and that additional items are needed, such as items screening for appetite, suicidal ideation, and sleep disturbances. This was in contrast to the study in the previous chapter that examined the construct validity of depression scales for PDC, where the GDS-30 was shown to have an acceptable convergent and discriminant validity, as well as other satisfactory psychometric properties such as high negative predictive value (90%), and clinical utility as assessed by the AUC estimate (0.80). However, there is no gold standard as to how to compare and contrast the findings of one validity study to another with differing aims. In other words, there is no tool to standardization magnitude of validity to allow comparability of findings from content to construct validity evidence.

Moreover, a majority of the experts agreed that some items are irrelevant and should be removed, particularly those referring to memory and cognitive impairment. This last was clearly compliant with the underlying aim of the PDC, to minimize the confounding effect of cognitive impairment due to dementia from depressive symptoms. However, of high interest is the fact that, at the item level, not all experts agreed to exclude items

referring to trouble with concentration or decision-making, other loaded cognitive components. This suggests that not all experts working with dementia and depression agree on the items included in the PDC. In other words, their understanding of depression in AD may not be similar, which highlights the importance of the aforementioned observational study (see Chapter 4).

From the item level and descriptive feedback, it is clear that the current GDS-30 formulation may not be optimal for use with the PDC-dAD. Several items need to be omitted and a few need to be added (see Table 18). In other words, a new assessment scale with an enhanced sensitivity, yet high specificity for screening for depression of AD, is needed.

Only one of the SMEs suggested adding an item screening for anhedonia, where at the item level analysis, 50% of the SMEs suggested to keep item number 2 (“Have you dropped many of your activities and interests?”) that is related to anhedonia. This shows the lack of concordance between raters and how the GDS-30 is assessed in comparison to the PDC. Additionally, this may have a relationship with the knowledge level of the SMEs with regard to the GDS-30.

Regarding the instructions for use of the GDS-30, the majority of the SMEs agreed that the GDS-30 was relatively easy to understand for mild cognitive deficit, but not for moderate to severe cognitive impairment. Apropos simplicity of response, a clear agreement was present for mild cognitive impairment that the scale’s response format is easy, but not as much for moderate to severe cognitive impairment. With regards to self-report versus an administrator-read approach, overall, for mild cognitive impairment, both methods were supported; however, for moderate to severe cognitive impairment, the

administrator-read approach was considered the most appropriate.

One shortcoming of the current study is that, due to time restrictions, we have missed an opportunity to assess the level of expertise/knowledge of the SMEs on the PDC, or for that matter, how often do they utilize the GDS-30, information that I would have wished to collect. However, based on *a priori* selection criteria of the SMEs, having expertise with dementia and depression, 2 had experience using the PDC; however for ethical concerns, on how this information was obtained, this knowledge was not provided. Nevertheless, these may be considered limitations given that we have provided the SMEs with the PDC symptoms and a copy of the GDS-30. However, the shortcoming of this study relies on the fact that SMEs did not rate the items of the shorter version of the GDS-30 (given that they saw all 30 GDS items when rating), and thus interpretation of results for the shorter versions should be done with caution.

A possible strength to this study, although arbitrary, is the inclusion of a heterogeneous range of experts, where we have included neurologists, psychiatrists, neuropsychologists, and clinicians and researchers. This could also account for the level of disagreement that we have observed. Thus, it would be important to gauge SMEs in each specialty separately, or run a comparative study. If for example, we had a group consisting solely of researchers with expertise on scale development, one may speculate that a different perspective would have emerged about the quality of the GDS-30.

The current study raises fascinating questions. For example, how should we interpret the items of the GDS-30 that are suggested to be included, in comparison to other GDS versions, such as the GDS-15? Would the GDS-15 stand as valid for the PDC-dAD if it were put to the test? Among the items to be excluded or revised according to the experts

opinion, items 4 (boredom), 14 (problem with memory) and 23 (“Do you feel that others are better off than you?”) are overlapping between the GDS-30 and GDS-15. Thus, by removing those items from the GDSs, the GDS-15 particularly will be shortened, and thus may not stand as valid for use with the PDC. By the same token, the same concern may apply to other shorter versions of the GDS-30. However, we have seen that the GDS with 8 items stands the test and is shown to have high specificity and acceptable sensitivity with high AUC value. Additionally, the AUC analysis of the shorter version of the GDS-30, the GDS-15, on the current data from the observational study showed that in fact the GDS-15 is capable of differentiating the PDC depressed from the non-depressed with an AUC comparable to the GDS-30.

By refining the total items to only those 8 items that have 83% or higher agreement for keeping (numbers in agreement for responses of 3 or 4), we may just fit the criteria for DSM-MDD, by simply omitting items of irritability and social isolation that are the highlights of the PDC-dAD. This is suggestive of the fact that further addition of items to the GDS with only 8 items is a must (see Table 18 for examples of additional items generated based on the suggestions from the SMEs), as most of the judges suggested, in order to better capture the PDC. On the other hand, the AUC analysis of the GDS with 8 items showed also a comparable AUC value to the GDS-30 for the PDC, suggesting that in order to improve our assessment approach, we may need to drop some items, but add items specific to the PDC in order to increase the AUC, or in other words the accuracy of the assessment scale. This last statistical result is consistent with the SMEs’ feedback, mentioned earlier.

Table 18. Possible items for development of the new assessment scale based on the SME comments, if symptoms were to be added for screening.

<i>No</i>	<i>Symptom</i>	<i>Items</i>	<i>Response</i>
1	Apathy	Have you lost interest in activities you used to enjoy?	Y/N
2	Appetite	Have you gained or lost significant weight?	Y/N
3	Fatigue	Does your tiredness limit your daily activities?	Y/N
4	Irritability	Do you feel that you are more argumentative and cranky than usual?	Y/N
5	Sleep	Do you have sleep difficulties?	Y/N
6	Suicide	Would you kill yourself if you have the chance?	Y/N

Additionally, given that the GDS is used with geriatric patients both with and without dementia, once the refinement is implemented, it would be imperative to re-name the new scale so it is distinguishable for the PDC-dAD.

Chapter 6. *Global conclusion*

Depression in AD adds to the heavy toll that dementia itself takes on the patient, care providers, and society. The current literature reveals that the nosology of depression in AD is varied, that depression has many risk factors and manifests in multiple ways. Understanding the presentation of depression in AD is complicated as is the neurobiology associated with the etiology of depression in AD. The Provisional Diagnostic Criteria (PDC) that emerged over a decade ago overcomes some of the limitations and concerns of the previously utilized criteria. The description of the PDC symptoms was phrased to avoid possible confounding of dementia symptoms such as diminished functional ability, language impairment, and cognitive disabilities. The PDC require three symptoms instead of five for diagnosis of depression, and symptoms are not required to be present nearly every day. The DSM-MDD item of diminished ability to think or concentrate was dropped.⁹ In turn, irritability and social isolation/withdrawal were added items. These were differences between depression diagnostic frameworks that contributed to the questions addressed in this dissertation regarding short and easily administered older-adult depression scales. Here I discuss the major findings, strengths and limitations, limitations of the evidence, and logical next steps.

Major findings

In my first study, a systematic review and meta-analysis of the available evidence, I examined the validity-evidence of the PDC. This study, using psychometric evidence (e.g., AUC, sensitivity, diagnostic overlap) in addition to epidemiological data provided supporting evidence around the validity of the PDC inferences, however the criteria need optimization. The epidemiological data showed that dAD was more prevalent than

indicated by the DSM-MDD or ICD (Chapter 3). Similarly, examination of the CARD charts (see Appendix I) and data obtained by the observational studies (Chapter 4) from the same clinic suggested a similar pattern (prevalence of depression by PDC: 26%; by DSM: 10%). Nonetheless, given that “irritability” item in the used diagnostic criteria form was missed, this may have an influence on the prevalence rate. Given the evidence from the literature, that close to 50% of depressed AD patients endorsed irritability (Chapter 3), one would have expected to see a slightly higher prevalence rate if the item was included.

The amalgam of the results from the review/meta-analysis with the content validity study suggests that the PDC can be further optimized. However, in the current state, with the non-significant difference on the MoCA between PDC+ and PDC-, the PDC does in fact perform one of the things that it is intended to do, minimize the confounding effects of cognitive symptoms of dementia from depression. This finding is consistent with the result from other studies showing non-significant difference between the PDC positives and the negatives in terms of global cognition.²¹³

From the observational study, lower cutoff scores for the GDS-30 and HDS-OA for the PDC use generally suggests that fewer symptoms are needed in contrast to published data with DSM criteria.^{344,345} In other words, the PDC appears to capture milder forms of depression. As a result, one can speculate that, given the PDC has the highest sensitivity in comparison to the DSM criteria in terms of capturing AD patients with depressive symptoms, and that the scales have been shown to have high specificity, the corroboration of the screening scores from any of the depression scales with the PDC should theoretically allow for optimal recognition of true depression in AD. In a different

vein, given the paucity of the evidence on the psychometric properties of the GDSIF-30, it is hard to make suggestions about comparability of our result to other studies using the GDSIF-30. In the observational study (Chapter 4), the physicians were blind to the depression scales' scores; the testers were blind to the symptoms endorsed by the patients on the PDC and, roughly 90% of the time, blinded to the depression diagnosis. I speculate that in the event that the physicians were aware of the scores on depression scales and the results from the neuropsychiatric inventory, the prevalence for depression as per the PDC would have been different. Of note, for clinical purposes, it is suggested that the clinicians corroborate outcomes from assessment scales, when available, to other clinical investigations when using the PDC.¹⁴⁹ Moreover, the true positives/false negatives would have been different, thus the result should be interpreted cautiously.

Overall, scales investigated here with the observational and content validity studies provide some degree of validity for use with the PDC, particularly with mild to mildly moderate cognitively impaired AD patients. All of the selected depression measures showed evidence of discriminant and convergent (construct) validity. They also showed an acceptable to high level of accuracy for detecting dAD in a homogeneous clinical sample mostly consisting of English speaking, mild probable AD as per the McKhann et al. 2011 clinical diagnostic criteria for Alzheimer's disease. Interestingly, the GDSIF-30 showed a higher level of accuracy in comparison to the patient rating scales (GDS-30 and HDS-OA). Moreover, when the GDS informant and the patient rating scales were combined, this accuracy value reached an optimal level in terms of sensitivity and specificity. But the fact that the AUC value for the GDSIF-30 and the GDS-GDS were the same suggests that the GDS-30 may have not added further accuracy to this

combination, suggesting that the utility of a scale with double the items, may be counterproductive. Thus, the shorter versions of the scales need to be examined (e.g., GDS-15 with GDSIF-15) in future studies, or a combination of the long informant with a shorter patient version (e.g., GDSIF-30 with GDS-15).

An important finding from the observational study was that the GDS-30 has poor specificity and a mediocre positive predictive value. It is somewhat counterintuitive that there are so many false positives when AD patients are usually expected to underreport their symptoms. There are a number of possible reasons for this result. First, although not consistent with other scales we have used, this many false positives could be due to the fact that clinician didn't have access to the result of screeners and a neuropsychiatric inventory to corroborate diagnosis. In other words, the true positives/false negatives may not be the real presentation of the findings. Second, it is possible that our sample was unique in that we had patients with mild to mildly moderate AD. Although less likely, one could speculate the possibility of an intact insight in these patients, suggesting that potentially they were reporting correct number of symptoms. Of course this is speculation given that we did not control for the level of insight, both directly via assessment scale and indirectly looking at the difference between patient and informant rating. Last, the result could have been an artifact that would have been lost if we had higher number of patients in the study.

As previously stated, the value of the scales vary as a function of the goal that they intend to accomplish, thus when the intention is to screen for depression, the aggregate measure with high sensitivity and specificity works, even with the presentation of a sizeable number of false positives. However, the aggregate scale may not be optimal, and

potentially a different weight or number of items can be given to each component of the scale. In this light however, one could speculate that self-report screening scales should be brief. In fact, as seen from the results of the GDS aggregate measure, a large number of items do not necessarily improve the test's accuracy; on the contrary, there is a sizeable risk of false positives.

Subsequently, these studies suggest that the GDS-30 and GDSIF-30 have validity for use with the PDC, however dropping and adding specific items in order to function optimally was supported by the internal consistency analyses, particularly with the succeeding content validity study of the GDS-30. By screening for depression, with either the GDSIF-30 or the shorter version of the GDS-30, triage at memory clinics could be facilitated with an eventual reduction in waiting list patients. In other words, patients with elevated depressive symptoms –otherwise known as at risk for depression– will be referred to geriatric psychiatrist rather than neurologist for evaluation of symptoms. In the end, the utility of a brief versus longer scale depends substantially on the purpose for its use. Perhaps, brief self-report scales could be of diagnostic aid given their low sensitivity, however given that they supply close to the same information that is in the PDC, this may not be the optimal approach. Therefore, additional items, to a limit, can help clinicians when there is uncertainty of a diagnosis. In these cases a short self-report can be optimally used with a full-version informant scale. Furthermore, a scale with a higher number of items would be more sensitive at detecting change if used at follow-up. These speculations warrant future longitudinal studies with a cross-sectional component for confirmation.

In line with the suggestion of greater brevity, the GDS-15, as suggested by the SMEs, also has shown validity, as seen via the AUC values obtained from the observational study. However, as per the internal consistency analysis (Chapter 4), this scale also needs revision for items. The shorter versions of the GDS, GDS with 8 items and GDS-30 without 4 items suggested by item removal from the content validity index, similarly yielded valid AUC values. However, their clinical utility remains to be tested, given that for these analyses, the research participants did not directly provide data.

Overall, as highlighted by the high level of internal consistency index, with a comparable number of items, both the GDS-30 and GDSIF-30 need content revision to optimally work with the PDC, either as a screener, or as a diagnostic aid. It is important to note that the PDC might also need optimization. Subsequently, the content validity study confirmed this concern by the number of items SMEs suggested for revision of the GDS-30, and not one SME suggested the revision of the PDC. This is interesting, given that it is possible that the experts were inadvertently biased toward considering the PDC as the only standard. In brief, although the depression scales are seen to be valid for use with the PDC, either as diagnostic aid, or screening tool, they could be all optimized.

Strengths and limitations

The first limitations of the observational study were that, the DSM diagnosis to corroborate PDC diagnosis was not used and that the study lacked a longitudinal component to confirm diagnosis or to assess test-retest reliability of the scales. Subsequently, inter- and intra-rater diagnostic agreement for the PDC was not accomplished given the limited availability of clinician and time-constraint. Although consistent with the literature, the majority of the participating clinicians from the UBCH-

CARD had expertise in neurology and geriatrics, which warrants the added use of geriatric psychiatrists in future studies. The second major limitation of our study was in the use of an incomplete diagnostic criterion. That is, the one we used in the observational study was missing an item, “irritability”. However the presence or absence of irritability could have been detected for diagnosis if the clinician were not blinded to screeners and the neuropsychiatry inventory results.

By and large, the sample consisted mostly of mild AD, and participants had a lower rate of depression with milder symptoms than the population of AD at large. This made the generalization of the results to the AD population at large difficult. On the other hand, the current sample was shown to have statistical power (>80%) for the ROC and correlational analyses, but a serious limitation affecting statistics examining multiple group differences and modifying variables. Nonetheless, examination of group differences was not the primary aim of the observational study and thus interpretation of these need to be done with caution.

The MoCA may be an optimal scale for screening cognitive impairment, but it may not be an optimal tool for detecting subtle cognitive differences between the PDC+ and the PDC-. In fact, the MoCA was never designed to delineate the depressed from the non-depressed. Besides, as other have reported, the impairment of the executive abilities,²¹³ a battery of neuropsychological tests sensitive for executive functioning is needed to see whether the PDC+ differ from the PDC- in terms of cognitive functioning.

Despite this fact, the lack of significant statistical difference between the PDC+ and PDC- in terms of the global cognitive score and the timed trail-making part of the MoCA may suggest that this is further evidence to support the validity of PDC, where its purpose

was to minimize the confounding effect of cognitive impairment from AD in depression diagnosis. However, given the literature and our study suggesting that potentially the PDC are covering a less severe depression, the lack of significant difference for these cognitive measures may not be an issue given that they are not optimal to detect subtle cognitive changes. Thus, given that the trail component of the MoCA is not validated to differentiate depressed from the non-depressed AD patients, this result should be interpreted with caution.

From the review study, a few questions remain. For example, with regards to those diagnosed as depressed by the DSM but not by the PDC, are they really depressed or are they false positives? The depression prevalence rate obtained from the observational study (26%) is below the range reported in the literature (Chapter 3). One possible reason for this low prevalence is that the observational study was mainly conducted over a limited time, and mostly over the spring/summer seasons where not only clinicians were taking vacation, but also patients were in better moods (potential seasonal effect). Another possibility, as previously mentioned, could be the missing item from the diagnostic form, and the absence of corroboration of clinical interviews with the scores from screeners and neuropsychiatric inventory.

In addition, the observational study showed a 100% completion rate when an administrator-read approach was used with a group of mild and mildly moderate cognitively impaired patients with diagnosis of possible and probable AD. This result may be in contrast to what was suggested by the SMEs from the content validity study, where self-report was suggested to be the optimal approach for mild AD but an

administrator-read approach is optimal for moderate to severe AD. This difference may need rectification in future cross-sectional studies.

Another global strength of the thesis is in its psychometric approach. Here convergent and discriminant validity-evidence were examined at once, thus providing concurrent validity-evidence. Moreover, both content and construct (convergent and discriminant) validity of the GDS-30 are present with the same diagnostic criteria to allow sound interpretation of its validity where statistical patient data are compared to experts interpretations. Furthermore, the content validity examination of the GDS-30 has been done by the authors of the screener;⁴⁵ however, the content validity study that was performed here is unique and specific to dAD that has not been done in the past.

Limitations of the evidence

Several points need addressing, such as concerns with differential diagnosis, sub-grouping of depression, and whether integration of depression into diagnostic frameworks for neurodegenerative disease is appropriate.

To enhance the validity-evidence around the PDC, longitudinal studies examining the criterion validity in terms of duration of symptoms and consistency of diagnosis were advocated, something that is presently lacking. In other words, the reliability of the PDC needs to be evaluated. This may lead to the refutation of the concern that dAD is less severe than DSM-MDD. In fact, what matters is that people with dAD should be reliably diagnosed on psychological as well as biological measures, with an eventual improvement of their quality of life. Nonetheless, there was evidence showing lower remission rates as measured by the PDC in comparison to the DSM-MDD.¹⁵² This is an interesting outcome, given that in the observational study no significant statistical

difference was observed between the PDC+ and PDC- in terms of medication use.

Alternatively, it is possible that the PDC+ were simply missed by the treating physician or that either the patients were not motivated enough or their symptoms were too severe to allow them participation in the study. Whether the PDC could differentiate depressed from the non-depressed patients with diagnosis of mild cognitive impairment due to AD adds validity to the criteria. Currently, there is only one study that used the PDC for validation of depression scales (MADRS and CSDD) with a sample of early-onset dementia of mixed diagnoses,³⁴⁶ suggesting there is much potential for using the PDC for depression diagnosis in dementia-spectrum. Moreover, differentiating depressed MCI from depression in older adults provides strength to the construct validity of the PDC.

Depression is an important complication/comorbidity observed along the entirety of the AD severity spectrum. For example, in the early stages of AD, when patients exhibit mild cognitive impairment (MCI due to AD, also called Cognitive Impairment No Dementia, CIND), as the evidence to date shows, the depression prevalence is equally high as in later stage of AD, notably mild to moderate AD,^{135,136} and heterogeneous. This has been suggested to be due to the variation in the assessment approaches to depression and diagnostic criteria utilized for mild cognitive impairment.³⁴⁷⁻³⁵⁰ For example, one large American longitudinal study of older individuals with CIND (65 years or older, N = 5092) showed that depression was the most prevalent neuropsychiatric syndrome at nearly 17%.³⁵¹ However, although inconsistently reported in the literature, other researchers have shown that depression/dysphoria as assessed via the NPI is the most prevalent neuropsychiatric syndrome in mild cognitive impairment at a frequency near to 25%.³⁵² This trend has been observed in other large and small cross-sectional studies

examining depression in mild cognitive impaired patients.³⁵³⁻³⁵⁵ These facts, the high prevalence of depression in older adults with cognitive dysfunction, and evidence suggesting depression being either a risk factor for dementia or being a prodromal stage of dementia, stimulate a greater need for understanding and evaluating depression in terms of the potential cognitive effects of AD. Thus, future epidemiological studies are necessary to examine the link between the depression risk factors and PDC-dAD.

Another important limitation in the validity-evidence around the PDC is that no one epidemiological study reported on the process of diagnosing dAD, and at most reported that the diagnosis was done by a psychiatrist blinded or not to the scales scores. This leads to the fact that important information as to how the PDC-dAD were implemented, and whether the PDC were followed to the point is missed. How have they excluded MDD patients (the PDC exclusion criteria) yet reported on the symptoms overlap between those diagnosed as depressed by the PDC and those diagnosed by the DSM-MDD criteria or by other means, is not clear. The potential impact that this information has on the available evidence highlights the need for future epidemiological studies and potential revision of the PDC.

The observational study aided in the selection of a screening tool for depression of AD. This could be used in specialty clinics and primary care settings for either case-finding or case-seeking. Knowledge gained from applying the scales and examining their relationship to PDC-dAD allows for an improved recognition of the phenomenology of depression with eventual superior management and care. The close relationship observed between depression and quality of life further suggests that a greater emphasis should be given to proper recognition and management of depression, which potentially provides

improvement in the quality of life of the dementia patients and caregivers. Also, this would potentially provide a better understanding of the potential relationship between depression and insight, which could be indirectly examined by the correlation between depression diagnosis and the discrepancy between patients and informant rating of quality of life scale scores.

Future studies would be needed to examine the difference between probable and possible AD in terms of the PDC symptoms, something that was not possible to accomplish with the observational study. For example, which symptom is endorsed more by the probable versus the possible AD person would be of interest to further differentiate these individuals, something that is currently not optimal. Furthermore, this may allow for a better understanding of dementias with underlying neurovascular degeneration.

With regards to subgrouping of depression, experts have suggested that it is likely that the PDC conceals a series of depressive syndromes (e.g., depression as a reaction to cognitive deficit, or recurrence of early and mid-life depression by DSM);¹⁴³ however, differentiating them may not necessarily augment the sensitivity or specificity of the diagnostic criteria. Nonetheless, it may add further validity and enhance the applicability of the provisional diagnostic criteria to other patient groups, such as those in nursing home settings. It is important to note that the observational study was limited to those patients living in the community. By subgrouping depressive syndromes, or for that matter the PDC, the external validity of the diagnostic criteria could be enhanced.

Last, reflecting on the idea of integration of depression into diagnostic frameworks for neurodegenerative disease may be daunting but not impossible. Since 2011,⁵⁸ experts from the National Institute on Aging–Alzheimer's Association (NIA-AA) have advocated

for a presentation of AD that may be more affective/behavioral than cognitive in nature, such that their guideline integrates changes in personality, behavior, or ‘comportment’—notably neuropsychiatric symptoms underlying depression—with criteria for diagnosis of dementia. This suggests that one of its presentations may be dAD, thus leading to further harmonization in terms of diagnosis of neurodegenerative illnesses with co-morbid affective or, generally neuropsychiatric, syndromes.

Logical next steps and recommendations

Currently the PDC is the best diagnostic criteria for depression of AD, however it remains a work in progress and needs optimization. From the systematic review, we have speculated that either sad mood or decreased positive affect (a symptom component of apathy) is the core symptom of depression. Although not surprising, the content validity study hinted at the possibility that experts may not agree on which symptoms better differentiate AD patients with depression from the non-depressed. The lack of agreement may reflect the individual variability between clinicians, or that clinician don’t have the same understanding of depression symptoms presenting in AD or that they don’t have the same training. However, from the observational study, in terms of neuropsychiatric symptoms, the PDC- differed from the PDC+ when irritability was present, but not by other symptoms.

This last observation hints at future directions for modification of the PDC and perhaps determining which symptom(s) are needed as the core depression symptom. For example, whether sad mood or decreased positive affect can play significantly as the core symptom of dAD remains a question for future studies. Additionally, as seen in Chapter 3, given the age effect on the aggregate prevalence rate, and the question of whether sad

mood may be absent in the severe stage of dementia, revising the PDC by taking into account age and dementia severity on the core depression symptoms is warranted. Conversely, the patient differentiation can be ameliorated by the use of a statistical item analysis with a larger sample size. In addition to content validity, item analysis would allow further refinement of the items and emergence of other symptoms to facilitate differentiation, which may add vigor to the already superior diagnostic criteria.

From the observational study, there was no significant effect of age, gender, and education of the patients, or the age and education level of the informants on the depression scales' scores. This is potentially due to the lack of sufficient age and education range in the sample, which may not allow the relationship between these variables and depression scores to be detected. However, this does not inform us as to whether informants are over-reporting symptoms due to the burden resulting from caring for AD patients or their actual aging, or patients are under-reporting given their cognitive impairment. Additionally, the quality assessment showed that as the quality of epidemiological studies improve the prevalence of depression increases. Thus future high-quality studies examining the difference between AD patients (patient-caregiver dyad) vs. normal older adults (patient-caregiver dyad) would help to better delineate this discrepancy.

In terms of the neurobiology and biomarkers for the PDC, extensive work is required. Given that the PDC were developed in part to deal with the heterogeneity that exists around DSM depression symptoms, it would be interesting to see whether neurobiological studies could potentially show the relationship between individual PDC symptoms and specific brain regions, or underlying neurotransmitter deficits.

The difference between the PDC+ and PDC- in terms of amyloid plaques and neurofibrillary tangles loading/burden needs to be examined. This may highlight the impact of these two core pathological markers of AD on depression of AD. Similarly, the difference between groups in terms of change in the white matter, or overall brain atrophy or the rate of atrophy, may help in better understanding of the pathophysiology, and identification of potential markers of depression in AD. This eventually may highlight the impact that depression has on AD progression and allow better monitoring of depression in AD patients who do not have the ability to report symptoms (to either a clinician or caregiver). Likewise, from the functionality perspective, several features could be examined. For example, although one study examined the difference between PDC groups by FDG-PET,²⁶⁷ confirming this finding as to whether the PDC+ significantly differ from the PDC- in terms of glucose metabolism remains to be replicated after the PDC were accepted as valid standard for diagnosis of depression in AD. Current evidence from depression by DSM criteria (i.e., MDD) suggests that poor glucose metabolism is associated with late-life depression and miserable mood.^{356,357} Similarly, to provide evidence of differential diagnosis between PDC+ and those diagnosed by DSM-MDD, examination of the neuro-metabolic differences is needed. Current evidence emanating from neuropsychological and neuroimaging studies have shown that dAD is associated with frontal lobe impairment (see chapter 3, study 1). However, this does not rule out the possibility of not the location but the anterograde or retrograde connection from frontal lobe as an underlying impairment in dAD. Functional magnetic resonance imaging (fMRI) studies would be needed to differentiate PDC+ from the DSM-MMD+ in terms of brain and behavior relationship. Given the attempt at

excluding cognitive confounding symptoms from the diagnostic algorithm, we could predict that brain regions responsible for affect regulation, including the amygdala and cerebellum, would be the differentiating factors, as opposed to the hippocampus that could be largely affected by both the neurodegenerative component of dementia as well as stress-related factors to depression.

Before discussing the recommendations on refining the GDS30 for use with the PDC, I would like to indicate that an alternative approach would be the development and validation of a new scale that reflects the PDC criteria. The reason for not pursuing the development of a new PDC based scale was the issue that the PDC criteria itself have yet to be established as a standard.

In terms of recommendations, GDS-30 or GDS-15, or either in combination with GDSIF-30, could be used as a screening tool in primary or tertiary clinics, given that they are short, easily given, and that have shown psychometric validity for use with the PDC. The GDS-30 or GDS-15 could function as a screening tool with mild to mildly moderate AD patients given the content validity results presented here. Furthermore, given the suggestion that when the MMSE score of 15 or higher is present, the chance of having lack of insight is less, thus the GDS-30 can be utilized without much difficulty with this individuals.³⁵⁸ Moreover, the GDS-30 is preferable over the shorter version of the scale in terms of research, given the higher number of items equal more variability, and that they are items that could show depression symptom correlation with the lack of insight, such as memory problems, trouble thinking, or noticing anything wrong with your mind.³⁵⁸ Benefits of using the GDS-30 or the shorter versions are in ameliorating case-findings when used as screener, given its relative high sensitivity. Although the informant

version maybe preferable in terms of psychometric, there are some limitations, A) the informant may or may not be present or have close relationship with the patient at the time of screening; and B) patient' personhood needs to be respected at all time, unless deemed incapable of consenting or providing coherent information. However, its advantage is in allowing better differentiation of depressed mood from subjective cognitive impairment in older adults, or it could be used as mentioned earlier, to corroborate findings. The screening for depression in primary and tertiary clinics globally would allow detecting cases that may have been otherwise missed, resulting in better treatment/management.

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Appendix A1. NIMH-Provisional Diagnostic Criteria of depression of AD (NIMH-PDC-dAD) (criteria used)

©

NIMH-PDC-dAD

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A. Three (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either depressed mood, or decreased positive affect or pleasure. ☐

Note: Do not include symptoms that, in your judgment, are clearly due to a medical condition other than AD, or are a direct result of non-mood related dementia symptoms (e.g., loss of weight due to difficulties with food intake).

Clinically significant depressed mood (e.g., depressed, sad, hopeless, discouraged, tearful) ☐

Decreased positive affect or pleasure in response to social contacts and usual activities ☐

Social isolation or withdrawal ☐

Disruption in appetite ☐

Disruption in sleep ☐

Psychomotor change (e.g., agitation or retardation) ☐

Fatigue or loss of energy ☐

Feeling of worthlessness, hopelessness, or excessive or inappropriate guilt ☐

Recurrent thoughts of death, suicidal ideation, plan or attempt ☐

B. All criteria are met for dementia of the Alzheimer's type (DSM-IV-TR) ☐

C. The symptoms cause clinically significant distress or disruption in functioning. ☐

D. The symptoms do not occur exclusively during the course of a delirium. ☐

F. The symptoms are not better accounted for by other conditions, such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of AD, anxiety disorders, or substance-related disorder. ☐

Specify if:

Co-occurring onset: if onset antedates or co-occurs with the AD symptoms _____

Post-AD onset: if onset occurs after AD symptoms _____

Specify:

With psychosis of AD _____

With other significant behavioral signs or symptoms _____

With past history of mood disorder _____

Olin et al. (2003). Provisional diagnostic criteria [...]. *Exper Rev. Neurotherapeutics* 3(1), 99-106.

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Appendix A2. NIMH-Provisional Diagnostic Criteria of depression of AD (NIMH-PDC-dAD) (true criteria)

Table 2. Provisional diagnostic criteria for depression of AD.

A. Three (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either depressed mood, or decreased positive affect or pleasure.

Note: Do not include symptoms that, in your judgment, are clearly due to a medical condition other than AD, or are a direct result of nonmood related dementia symptoms (e.g., loss of weight due to difficulties with food intake).

- Clinically significant depressed mood (e.g., depressed, sad, hopeless, discouraged, tearful)
- Decreased positive affect or pleasure in response to social contacts and usual activities
- Social isolation or withdrawal
- Disruption in appetite
- Disruption in sleep
- Psychomotor changes (e.g., agitation or retardation)
- Irritability
- Fatigue or loss of energy
- Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
- Recurrent thoughts of death, suicidal ideation, plan or attempt

B. All criteria are met for dementia of the Alzheimer's type (DSM-IV-TR).

C. The symptoms cause clinically significant distress or disruption in functioning.

D. The symptoms do not occur exclusively during the course of a delirium.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication).

F. The symptoms are not better accounted for by other conditions, such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of AD, anxiety disorders, or substance-related disorder.

Specify if:

Co-occurring onset: if onset antedates or co-occurs with the AD symptoms

PostAD onset: if onset occurs after AD symptoms

Specify:

With psychosis of AD

With other significant behavioral signs or symptoms

With past history of mood disorder

AD: Alzheimer's disease; DSM: *Diagnostic and Statistical Manual of Mental Disorders*.

Note: from Olin et al 2003. Provisional Diagnostic Criteria [...] Expert Review Neurotherapeutics 3(1): 99-106.

Appendix B. Dementia diagnostic criteria

a) The operational definition for diagnosis of AD⁵⁸

Meeting criteria for dementia and in addition, must meet the following:

A. Insidious onset;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following:

a) Amnestic presentation, particularly recall. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, such as

b) Non-amnestic presentations (Language presentation, Visuospatial presentation, or Executive dysfunction)⁵⁸

b) Operational definition for diagnosis of possible AD⁵⁸ core clinical criteria

Atypical course:

Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline,

Or

Etiologically mixed presentation:

Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition Note: A diagnosis of “possible AD” by the 1984 NINCDS-ADRDA criteria [1] would not necessarily meet the current criteria for possible AD dementia. Such a patient would need to be re-evaluated.

Appendix C. Observational Study Selection criteria

- *INCLUSION CRITERIA:*
 - Meeting criteria for primary possible and probable mild or moderate AD⁵⁸ as per 2011 core clinical criteria
 - Ability to communicate in English
 - Has a knowledgeable informant

- *EXCLUSION CRITERIA:*
 - Antipsychotics regimen
 - Current alcohol or drug abuse
 - Recent (<12mo) head injury
 - Presence of active delirium or psychosis
 - A history of other psychiatric disorder
 - Being enrolled in clinical trial (pharmacological or non-pharmacological)
 - Any medical condition that in the opinion of the clinician could induce behavioral or mood changes, e.g. acute infections, nutrient deficiencies

Appendix D. Patient enrollment and recruitment procedure

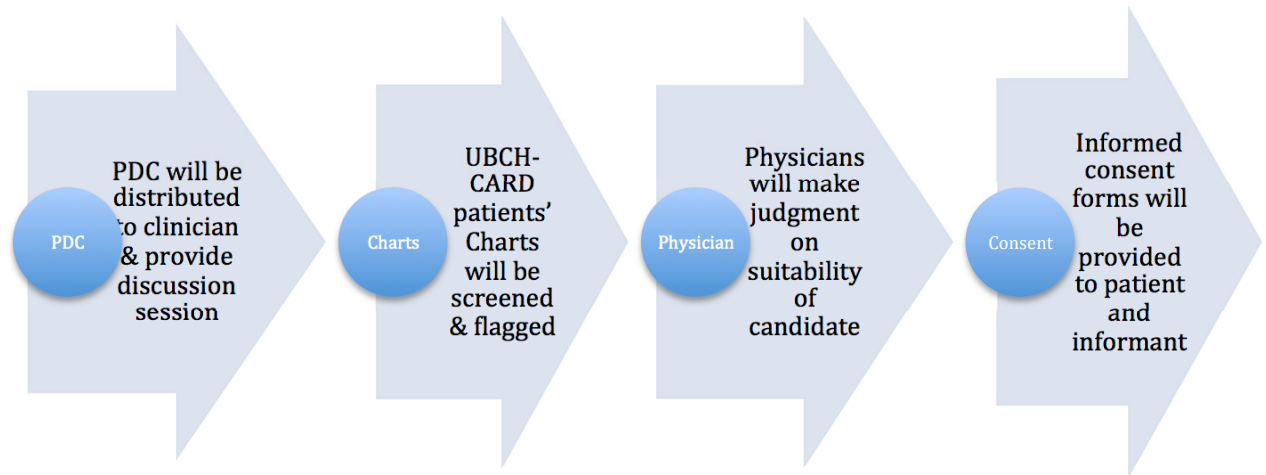


Figure 8. Time-line for the observational study (~6 months)- Pre-enrollment

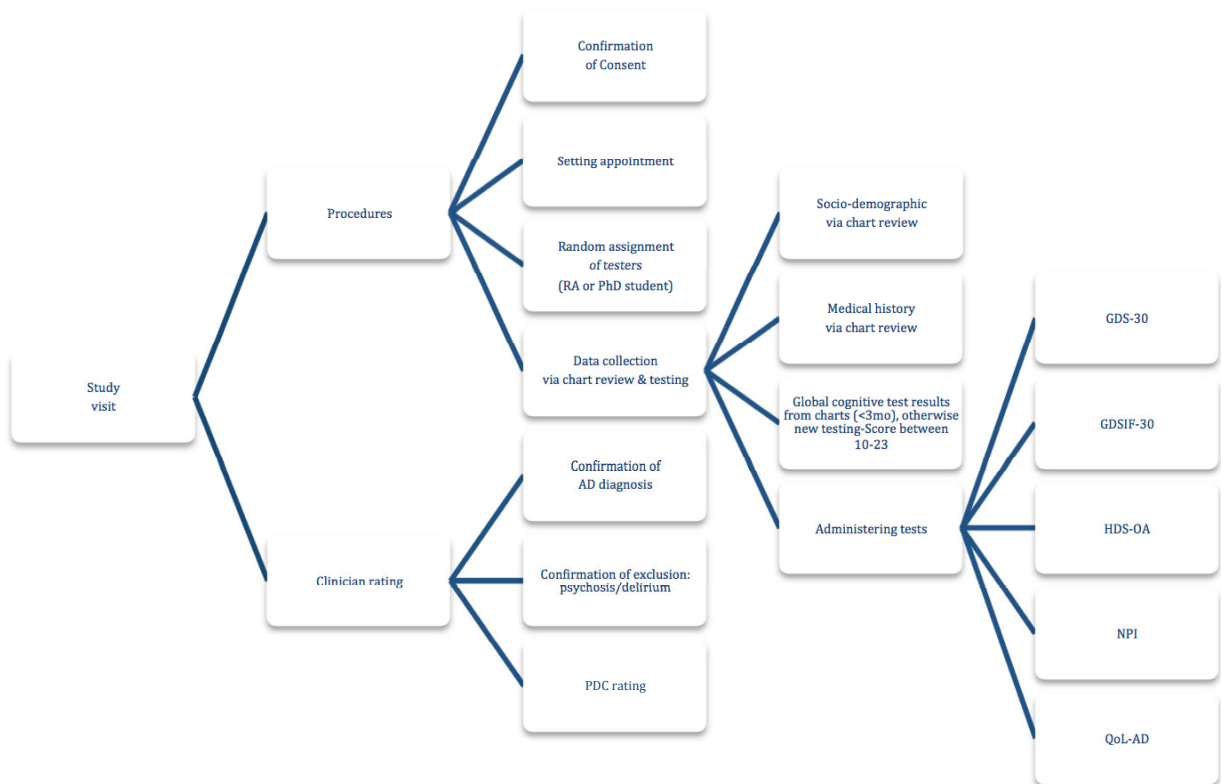


Figure 9. Time-line for the observational study (~6 months)- Study visit

Table 19. Order for administration of the scales

Testing time			
Order	Patient	Caregiver/proxy	Time
1)	GDS-30	GDSIF-30	10 min
2)	QOL-AD	NPI	45 min
3)	HDS-OA	QOL-AD	15 min
Total time needed:			~70min

Note: GDS-30: Geriatric Depression Scale-30- item; GDSIF-30: Geriatric Depression Scale for Informant-30-item; HDS-OA: Hubley Depression Scale for Older Adults; QOL-AD: Quality of Life for Alzheimer’s Disease; NPI: Neuropsychiatric Inventory.

Appendix E1. Hubley Depression Scale for Older Adults (HDS-OA)

HUBLEY DEPRESSION SCALE FOR OLDER ADULTS (HDS-OA)
(Hubley, 1998)

The following questions have to do with changes that might have taken place in your life recently. For each question, please circle the answer (yes or no) that best applies to you.

1. Over the past two weeks: Have you
felt useful and needed?.....yes/no
2. Over the past two weeks: Have you
noticed any changes in your appetite?....yes/no
(examples: you didn't feel like eating, or
you felt hungrier than usual)
3. Over the past two weeks: Have you
felt full of energy?.....yes/no
4. Over the past two weeks: Have you
often felt sad and downhearted?.....yes/no
5. Over the past two weeks: Have your
sleeping patterns changed?.....yes/no
(examples: you have been waking up in the
middle of the night or unusually early)
6. Over the past two weeks: Have you
had difficulty concentrating?.....yes/no
7. Over the past two weeks: Have you
been interested in your usual
activities?.....yes/no
8. Over the past two weeks: Have you
felt that you (or others) would be
better off if you were dead?.....yes/no
9. Over the past two weeks: Have you
become irritated more easily than
usual?.....yes/no

10. Over the past two weeks: Have you
felt different than you usually do?.....yes/no
(examples: you felt unusually restless, or
you felt like you were moving in slow motion)
11. Over the past two weeks: Has
anyone mentioned to you that you
don't look or seem your usual self?.....yes/no
12. Over the past two weeks: Have you
enjoyed doing things as much as ever?....yes/no
13. Over the past two weeks: Have you
felt like everything was your fault?.....yes/no
14. Over the past two weeks: Have you
frequently felt like crying?.....yes/no
15. Over the past two weeks: Have you
found it harder than usual to make
decisions?.....yes/no
16. Over the past two weeks: Have you
thought that the future looks
hopeless?.....yes/no

TOTAL SCORE: _____

Additional Questions:

- A. Have you started taking a new
medication in the past month?.....yes/no
- B. Are you grieving for someone
who has died in the past two
months?.....yes/no

Dr. Anita M. Hubley, University of British Columbia, Vancouver, Canada.

HUBLEY DEPRESSION SCALE FOR OLDER ADULTS (HDS-OA)
(Hubley, 1998) (KEY)

The following questions have to do with changes that might have taken place in your life recently. For each question, please circle the answer (yes or no) that best applies to you.

1. Over the past two weeks: Have you
felt useful and needed?.....yes/no
2. Over the past two weeks: Have you
noticed any changes in your appetite?....yes/no
(examples: you didn't feel like eating, or
you felt hungrier than usual)
3. Over the past two weeks: Have you
felt full of energy?.....yes/no
4. Over the past two weeks: Have you
often felt sad and downhearted?.....yes/no
5. Over the past two weeks: Have your
sleeping patterns changed?.....yes/no
(examples: you have been waking up in the
middle of the night or unusually early)
6. Over the past two weeks: Have you
had difficulty concentrating?.....yes/no
7. Over the past two weeks: Have you
been interested in your usual
activities?.....yes/no
8. Over the past two weeks: Have you
felt that you (or others) would be
better off if you were dead?.....yes/no
9. Over the past two weeks: Have you
become irritated more easily than
usual?.....yes/no

10. Over the past two weeks: Have you felt different than you usually do?.....yes/no
(examples: you felt unusually restless, or you felt like you were moving in slow motion)
11. Over the past two weeks: Has anyone mentioned to you that you don't look or seem your usual self?.....yes/no
12. Over the past two weeks: Have you enjoyed doing things as much as ever?....yes/no
13. Over the past two weeks: Have you felt like everything was your fault?.....yes/no
14. Over the past two weeks: Have you frequently felt like crying?.....yes/no
15. Over the past two weeks: Have you found it harder than usual to make decisions?.....yes/no
16. Over the past two weeks: Have you thought that the future looks hopeless?.....yes/no

TOTAL SCORE: _____

Additional Questions:

Q.A: Answering "yes" to Question A raises the possibility that any endorsed depressive symptoms *may be due* to contraindications of medication.

Q.B: Answering "yes" to Question B raises the possibility that any endorsed depressive symptoms *may be due* to bereavement rather than major depression.

Other exclusionary criteria (i.e., presence of a mixed episode/mania, gen. medical cond., signif. distress or impairment of social or occup. functioning) are not addressed here as they may be better assessed during a diag. interview.

Dr. Anita M. Hubley, University of British Columbia, Vancouver, Canada.

Appendix E2. Depression scales: GDS for Informant-30-item (GDSIF-30)

Circle the best answer for how you think the patient has felt in the last week

Are they basically satisfied with their life?	YES	NO
Have they dropped many of their activities and interests?	YES	NO
Do they feel that their life is empty?	YES	NO
Do they often get bored?	YES	NO
Are they hopeful about their future?	YES	NO
Are they bothered by thoughts they can't get out of their head?	YES	NO
Are they in good spirits most of the time?	YES	NO
Are they afraid that something bad is going to happen to them?	YES	NO
Do they feel happy most of the time?	YES	NO
Do they feel helpless?	YES	NO
Do they often get restless and fidgety?	YES	NO
Do they prefer to stay at home rather than going out and doing new things?	YES	NO
Do they frequently worry about the future?	YES	NO
Do they feel they have more problems with memory than most?	YES	NO
Do they think it is wonderful to be alive now?	YES	NO
Do they feel downhearted and blue?	YES	NO
Do they feel pretty worthless the way they are now?	YES	NO
Do they worry a lot about the past?	YES	NO
Do they find life very exciting?	YES	NO
Is it hard for them to get started on new projects?	YES	NO
Do they feel full of energy?	YES	NO
Do they feel that their situation is hopeless?	YES	NO
Do they think that most people are better off than they are?	YES	NO
Do they frequently get upset over little things?	YES	NO
Do they frequently feel like crying?	YES	NO
Do they have trouble concentrating?	YES	NO
Do they enjoy getting up in the morning?	YES	NO
Do they prefer to avoid social gatherings?	YES	NO
Is it easy for them to make decisions?	YES	NO
Is their mind as clear as it used to be?	YES	NO

Appendix E3. The Geriatric Depression Scale-30-item (GDS-30)

Instructions: Please circle the best answer for how you felt over the past week.

1. Are you basically satisfied with your life?	Yes	No
2. Have you dropped many of your activities and interests?	Yes	No
3. Do you feel that your life is empty?	Yes	No
4. Do you often get bored?	Yes	No
5. Are you hopeful about the future?	Yes	No
6. Are you bothered by thoughts you can't get out of your head?	Yes	No
7. Are you in good spirits most of the time?	Yes	No
8. Are you afraid that something bad is going to happen to you?	Yes	No
9. Do you feel happy most of the time?	Yes	No
10. Do you often feel helpless?	Yes	No
11. Do you often get restless and fidgety?	Yes	No
12. Do you prefer to stay at home, rather than going out and doing new things?	Yes	No
13. Do you frequently worry about the future?	Yes	No
14. Do you feel you have more problems with memory than most?	Yes	No
15. Do you think it is wonderful to be alive now?	Yes	No
16. Do you often feel downhearted and blue?	Yes	No
17. Do you feel pretty worthless the way you are now?	Yes	No
18. Do you worry a lot about the past?	Yes	No
19. Do you find life very exciting?	Yes	No
20. Is it hard for you to get started on new projects?	Yes	No
21. Do you feel full of energy?	Yes	No
22. Do you feel that your situation is hopeless?	Yes	No
23. Do you think that most people are better off than you are?	Yes	No
24. Do you frequently get upset over little things?	Yes	No
25. Do you frequently feel like crying?	Yes	No
26. Do you have trouble concentrating?	Yes	No
27. Do you enjoy getting up in the morning?	Yes	No
28. Do you prefer to avoid social gatherings?	Yes	No
29. Is it easy for you to make decisions?	Yes	No
30. Is your mind as clear as it used to be?	Yes	No

Scoring for the Geriatric Depression Scale (GDS)

In scoring the Geriatric Depression Scale, each item is scored 0 or 1 depending upon whether the item is worded positively or negatively. The total score on the scale ranges from 0 to 30.

For items 2-4, 6, 8, 10-14, 16-18, 20, 22-26, 28 the scoring is:

- Yes = 1
- No = 0

Items 1, 5, 7, 9, 15, 19, 21, 27, 29, 30 are reverse scored as follows:

- No = 1
- Yes = 0

Appendix F. Neuropsychiatric Inventory

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A. DELUSIONS

(NA)

Does the patient have beliefs that you know are not true (for example, insisting that people are trying to harm him/her or steal from him/her)? Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient believe that he/she is in danger - that others are planning to hurt him/her? _____
2. Does the patient believe that others are stealing from him/her? _____
3. Does the patient believe that his/her spouse is having an affair? _____
4. Does the patient believe that unwelcome guests are living in his/her house? _____
5. Does the patient believe that his/her spouse or others are not who they claim to be? _____
6. Does the patient believe that his/her house is not his/her home? _____
7. Does the patient believe that family members plan to abandon him/her? _____
8. Does the patient believe that television or magazine figures are actually present in the home? [Does he/she try to talk or interact with them?] _____
9. Does the patient believe any other unusual things that I haven't asked about? _____

If the screening question is confirmed, determine the frequency and severity of the delusions.

- Frequency:
1. Occasionally - less than once per week.
 2. Often - about once per week.
 3. Frequently - several times per week but less than every day.
 4. Very frequently - once or more per day.
- Severity:
1. Mild - delusions present but seem harmless and produce little distress in the patient.
 2. Moderate - delusions are distressing and disruptive.
 3. Marked - delusions are very disruptive and are a major source of behavioral disruption. [If PRN medications are prescribed, their use signals that the delusions are of marked severity.]
- Distress:
- How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

B. HALLUCINATIONS**(NA)**

Does the patient have hallucinations such as seeing false visions or hearing false voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive; rather we are asking if the patient actually has abnormal experiences of sounds or visions.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient describe hearing voices or act as if he/she hears voices? _____
2. Does the patient talk to people who are not there? _____
3. Does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc)? _____
4. Does the patient report smelling odors not smelled by others? _____
5. Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her? _____
6. Does the patient describe tastes that are without any known cause? _____
7. Does the patient describe any other unusual sensory experiences? _____

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

- Frequency:
1. Occasionally – less than once per week.
 2. Often – about once per week.
 3. Frequently – several times per week but less than every day.
 4. Very frequently – once or more per day.

- Severity:
1. Mild – hallucinations are present but harmless and cause little distress for the patient.
 2. Moderate – hallucinations are distressing and are disruptive to the patient.
 3. Marked – hallucinations are very disruptive and are a major source of behavioral disturbance. PRN medications may be required to control them.

- Distress:
- How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

C. AGITATION/AGGRESSION**(NA)**

Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes? _____
2. Is the patient stubborn, having to have things his/her way? _____
3. Is the patient uncooperative, resistive to help from others? _____
4. Does the patient have any other behaviors that make him/her hard to handle? _____
5. Does the patient shout or curse angrily? _____
6. Does the patient slam doors, kick furniture, throw things? _____
7. Does the patient attempt to hurt or hit others? _____
8. Does the patient have any other aggressive or agitated behaviors? _____

If the screening question is confirmed, determine the frequency and severity of the agitation/aggression.

- Frequency:
1. Occasionally - less than once per week.
 2. Often - about once per week.
 3. Frequently - several times per week but less than daily.
 4. Very frequently - once or more per day.

- Severity:
1. Mild - agitation is disruptive but can be managed with redirection or reassurance.
 2. Moderate - agitation is disruptive and difficult to redirect or control.
 3. Marked - agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.

- Distress: How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

D. DEPRESSION/DYSPHORIA**(NA)**

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have periods of tearfulness or sobbing that seem to indicate sadness? _____
2. Does the patient say, or act as if, he/she is sad or in low spirits? _____
3. Does the patient put him/herself down or say that he/she feels like a failure? _____
4. Does the patient say that he/she is a bad person or deserves to be punished? _____
5. Does the patient seem very discouraged or say that he/she has no future? _____
6. Does the patient say he/she is a burden to the family or that the family would be better off without him/her? _____
7. Does the patient express a wish for death or talk about killing himself/herself? _____
8. Does the patient show any other signs of depression or sadness? _____

If the screening question is confirmed, determine the frequency and severity of the depression/dysphoria.

- Frequency:
1. Occasionally – less than once per week.
 2. Often – about once per week.
 3. Frequently – several times per week but less than every day.
 4. Very frequently – essentially continuously present.

- Severity:
1. Mild – depression is distressing but usually responds to redirection or reassurance.
 2. Moderate – depression is distressing; depressive symptoms are spontaneously voiced by the patient and difficult to alleviate.
 3. Marked – depression is very distressing and a major source of suffering for the patient.

- Distress: How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

E. ANXIETY**(NA)**

Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient say that he/she is worried about planned events? _____
2. Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense? _____
3. Does the patient have periods of [or complain of] shortness of breath, gasping, or sighing for no apparent reason other than nervousness? _____
4. Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? [Symptoms not explained by ill health] _____
5. Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds? _____
6. Does the patient become nervous and upset when separated from you [or his/her caregiver]? [Does he/she cling to you to keep from being separated?] _____
7. Does the patient show any other signs of anxiety? _____

If the screening question is confirmed, determine the frequency and severity of the anxiety.

- Frequency:
1. Occasionally - less than once per week.
 2. Often - about once per week.
 3. Frequently - several times per week but less than every day.
 4. Very frequently - once or more per day.

- Severity:
1. Mild - anxiety is distressing but usually responds to redirection or reassurance.
 2. Moderate - anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate.
 3. Marked - anxiety is very distressing and a major source of suffering for the patient.

- Distress:
- How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

F. ELATION/EUPHORIA**(NA)**

Does the patient seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the patient has a persistent and abnormally good mood or finds humor where others do not.

NO (If no, proceed to next screening question).

YES (If yes, proceed to subquestions).

1. Does the patient appear to feel too good or to be too happy, different from his/her usual self? _____
2. Does the patient find humor and laugh at things that others do not find funny? _____
3. Does the patient seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)? _____
4. Does the patient tell jokes or make remarks that are not funny to others but seem funny to him/her? _____
5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it? _____
6. Does the patient "talk big" or claim to have more abilities or wealth than is true? _____
7. Does the patient show any other signs of feeling too good or being too happy? _____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

Frequency:

1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - essentially continuously present.

Severity:

1. Mild - elation is notable to friends and family but is not disruptive.
2. Moderate - elation is notably abnormal.
3. Marked - elation is very pronounced; patient is euphoric and finds nearly everything to be humorous.

Distress:

How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

G. APATHY/INDIFFERENCE**(NA)**

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or does he/she lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient seem less spontaneous and less active than usual? _____
2. Is the patient less likely to initiate a conversation? _____
3. Is the patient less affectionate or lacking in emotions when compared to his/her usual self? _____
4. Does the patient contribute less to household chores? _____
5. Does the patient seem less interested in the activities and plans of others? _____
6. Has the patient lost interest in friends and family members? _____
7. Is the patient less enthusiastic about his/her usual interests? _____
8. Does the patient show any other signs that he/she doesn't care about doing new things? _____

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

- Frequency:
1. Occasionally – less than once per week.
 2. Often – about once per week.
 3. Frequently – several times per week but less than every day.
 4. Very frequently – nearly always present.

- Severity:
1. Mild – apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behavior; patient responds to suggestions to engage in activities.
 2. Moderate – apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
 3. Marked – apathy is very evident and usually fails to respond to any encouragement or external events.

- Distress:
- How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

H. DISINHIBITION

(NA)

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient act impulsively without appearing to consider the consequences? _____
2. Does the patient talk to total strangers as if he/she knew them? _____
3. Does the patient say things to people that are insensitive or hurt their feelings? _____
4. Does the patient say crude things or make sexual remarks that he/she would not usually have said? _____
5. Does the patient talk openly about very personal or private matters not usually discussed in public? _____
6. Does the patient take liberties or touch or hug others in way that is out of character for him/her? _____
7. Does the patient show any other signs of loss of control of his/her impulses? _____

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

- Frequency:
1. Occasionally – less than once per week.
 2. Often – about once per week.
 3. Frequently – several times per week but less than every day.
 4. Very frequently – essentially continuously present.

- Severity:
1. Mild – disinhibition is notable but usually responds to redirection and guidance.
 2. Moderate – disinhibition is very evident and difficult to overcome by the caregiver.
 3. Marked – disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress.

- Distress:
- How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

I. IRRITABILITY/LABILITY

(NA)

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

NO (If no, proceed to next screening question).

YES (If yes, proceed to subquestions).

1. Does the patient have a bad temper, "flying off the handle" easily over little things? _____
2. Does the patient rapidly change moods from one to another, being fine one minute and angry the next? _____
3. Does the patient have sudden flashes of anger? _____
4. Is the patient impatient, having trouble coping with delays or waiting for planned activities? _____
5. Is the patient cranky and irritable? _____
6. Is the patient argumentative and difficult to get along with? _____
7. Does the patient show any other signs of irritability? _____

If the screening question is confirmed, determine the frequency and severity of the irritability/lability.

Frequency:

1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - essentially continuously present.

Severity:

1. Mild - irritability or lability is notable but usually responds to redirection and reassurance.
2. Moderate - irritability and lability are very evident and difficult to overcome by the caregiver.
3. Marked - irritability and lability are very evident; they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

Distress:

How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

J. ABERRANT MOTOR BEHAVIOR**(NA)**

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

NO (If no, proceed to next screening question).

YES (If yes, proceed to subquestions).

1. Does the patient pace around the house without apparent purpose? _____
2. Does the patient rummage around opening and unpacking drawers or closets? _____
3. Does the patient repeatedly put on and take off clothing? _____
4. Does the patient have repetitive activities or "habits" that he/she performs over and over? _____
5. Does the patient engage in repetitive activities such as handling buttons, picking, wrapping string, etc? _____
6. Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot? _____
7. Does the patient do any other activities over and over? _____

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

- Frequency:
1. Occasionally - less than once per week.
 2. Often - about once per week.
 3. Frequently - several times per week but less than every day.
 4. Very frequently - essentially continuously present.

- Severity:
1. Mild - abnormal motor activity is notable but produces little interference with daily routines.
 2. Moderate - abnormal motor activity is very evident; can be overcome by the caregiver.
 3. Marked - abnormal motor activity is very evident, usually fails to respond to any intervention by the caregiver and is a major source of distress.

- Distress:
- How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

K. SLEEP AND NIGHTTIME BEHAVIOR DISORDERS**(NA)**

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have difficulty falling asleep? _____
2. Does the patient get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? _____
3. Does the patient wander, pace, or get involved in inappropriate activities at night? _____
4. Does the patient awaken you during the night? _____
5. Does the patient wake up at night, dress, and plan to go out, thinking that it is morning and time to start the day? _____
6. Does the patient awaken too early in the morning (earlier than was his/her habit)? _____
7. Does the patient sleep excessively during the day? _____
8. Does the patient have any other nighttime behaviors that bother you that we haven't talked about? _____

If the screening question is confirmed, determine the frequency and severity of the nighttime behavior.

- Frequency:
1. Occasionally – less than once per week.
 2. Often – about once per week.
 3. Frequently – several times per week but less than every day.
 4. Very frequently – once or more per day (every night).

- Severity:
1. Mild – nighttime behaviors occur but they are not particularly disruptive.
 2. Moderate – nighttime behaviors occur and disturb the patient and the sleep of the caregiver; more than one type of nighttime behavior may be present.
 3. Marked – nighttime behaviors occur; several types of nighttime behavior may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed.

- Distress: How emotionally distressing do you find this behavior?
0. Not at all
 1. Minimally
 2. Mildly
 3. Moderately
 4. Severely
 5. Very severely or extremely

L. APPETITE AND EATING DISORDERS

(NA)

Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

NO (If no, proceed to next screening question).

YES (If yes, proceed to subquestions).

1. Has he/she had a loss of appetite? _____
2. Has he/she had an increase in appetite? _____
3. Has he/she had a loss of weight? _____
4. Has he/she gained weight? _____
5. Has he/she had a change in eating behavior such as putting too much food in his/her mouth at once? _____
6. Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food? _____
7. Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order? _____
8. Have there been any other changes in appetite or eating that I haven't asked about? _____

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

Frequency:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day or continuously.

Severity:

1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.
2. Moderate – changes in appetite or eating are present and cause minor fluctuations in weight.
3. Marked – obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient.

Distress:

How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

NPI	Neuropsychiatric Inventory Scoring Summary
-----	--

CENTER NUMBER	SCREENING NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT	DATE
□□□	□□□□□	□□□□	□□□ F M L	□□	□□□ M D Y

Please transcribe appropriate categories from the NPI Worksheet into the boxes provided. For each domain: If symptoms of a domain did not apply, check the "N/A" box. If symptoms of a domain were absent, check the "0" box. If symptoms of a domain were present, check one score each for Frequency and Severity. Multiply Frequency score x Severity score and enter the product in the space provided. Total all Frequency x Severity scores and record the Total Score below. If symptoms of a domain were present, check one score for Distress; total all distress scores for a summary score.	Rater's Initials: □□□
---	-------------------------------------

DOMAIN	N/A	ABSENT	FREQUENCY	SEVERITY	FREQUENCY X SEVERITY	OCCUPATIONAL DISRUPTION
A. Delusions	□	0	1234	123	□ □	012345
B. Hallucinations	□	0	1234	123	□ □	012345
C. Agitation/Aggression	□	0	1234	123	□ □	012345
D. Depression	□	0	1234	123	□ □	012345
E. Anxiety	□	0	1234	123	□ □	012345
F. Elation/Euphoria	□	0	1234	123	□ □	012345
G. Apathy/Indifference	□	0	1234	123	□ □	012345
H. Disinhibition	□	0	1234	123	□ □	012345
I. Irritability/Liability	□	0	1234	123	□ □	012345
J. Aberrant Motor Behavior	□	0	1234	123	□ □	012345
TOTAL SCORE:					□□□	□□
K. Nighttime Behavior	□	0	1234	123	□ □	012345
L. Appetite/Eating Change	□	0	1234	123	□ □	012345



Neuropsychiatric Inventory

Worksheet

Directions: Read all items from the NPI "Instructions for Administration of the NPI". Mark Caregiver's responses on this worksheet before scoring the Frequency, Severity, and Caregiver Distress for each item.

A. DELUSIONS: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Fear of harm ☐ 2. Fear of theft ☐ 3. Spousal affair ☐ 4. Phantom boarder ☐ 5. Spouse imposter ☐ 6. House not home ☐ 7. Fear of abandonment ☐ 8. Talks to TV, etc. ☐ 9. Other _____	B. HALLUCINATIONS: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Hears voices ☐ 2. Talks to people not there ☐ 3. Sees things not there ☐ 4. Smells things not there ☐ 5. Feels things not there ☐ 6. Unusual taste sensations ☐ 7. Other _____
C. AGITATION/AGGRESSION: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Upset with caregiver; resists ADL's ☐ 2. Stubbornness ☐ 3. Uncooperative; resists help ☐ 4. Hard to handle ☐ 5. Cursing or shouting angrily ☐ 6. Slams doors; kicks, throws things ☐ 7. Hits, harms others ☐ 8. Other _____	D. DEPRESSION/DYSPHORIA: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Tearful and sobbing ☐ 2. States, acts as if sad ☐ 3. Puts self down, feels like failure ☐ 4. "Bad person", deserves punishment ☐ 5. Discouraged, no future ☐ 6. Burden to family ☐ 7. Talks about dying, killing self ☐ 8. Other _____
E. ANXIETY: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Worries about planned events ☐ 2. Feels shaky, tense ☐ 3. Sobs, sighs, gasps ☐ 4. Racing heart, "butterflies" ☐ 5. Phobic avoidance ☐ 6. Separation anxiety ☐ 7. Other _____	F. ELATION/EUPHORIA: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Feels too good, too happy ☐ 2. Abnormal humor ☐ 3. Childish, laughs inappropriately ☐ 4. Jokes or remarks not funny to others ☐ 5. Childish pranks ☐ 6. Talks "big", grandiose ☐ 7. Other _____

G. APATHY/INDIFFERENCE: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Less spontaneous or active ☐ 2. Less likely to initiate conversation ☐ 3. Less affectionate, lacking emotions ☐ 4. Contributes less to household chores ☐ 5. Less interested in others ☐ 6. Lost interest in friends or family ☐ 7. Less enthusiastic about interests ☐ 8. Other _____	H. DISINHIBITION: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Acts impulsively ☐ 2. Excessively familiar with strangers ☐ 3. Insensitive or hurtful remarks ☐ 4. Crude or sexual remarks ☐ 5. Talks openly of private matters ☐ 6. Inappropriate touching of others ☐ 7. Other _____
I. IRRITABILITY: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Bad temper, "flies off handle" easily ☐ 2. Rapid changes in mood ☐ 3. Sudden flashes of anger ☐ 4. Impatient, trouble coping with delays ☐ 5. Cranky, irritable ☐ 6. Argues, difficult to get along with ☐ 7. Other _____	J. ABERRANT MOTOR BEHAVIOR: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Paces without purpose ☐ 2. Opens or unpacks closets or drawers ☐ 3. Repeatedly dresses and undresses ☐ 4. Repetitive activities or "habits" ☐ 5. Handling, picking, wrapping behavior ☐ 6. Excessively fidgety ☐ 7. Other _____
K. NIGHTTIME BEHAVIORS: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Difficulty falling asleep ☐ 2. Up during the night ☐ 3. Wanders, paces, inappropriate activity ☐ 4. Awakens others at night ☐ 5. Wakes and dresses to go out at night ☐ 6. Early morning awakening ☐ 7. Sleeps excessively during the day ☐ 8. Other _____	L. APPETITE/EATING BEHAVIORS: Y N N/A Frequency _____ Severity _____ Distress _____ ☐ 1. Loss of appetite ☐ 2. Increased appetite ☐ 3. Weight loss ☐ 4. Weight gain ☐ 5. Change in eating habits ☐ 6. Change in food preferences ☐ 7. Eating rituals ☐ 8. Other _____

Appendix G. Quality of Life Scale for AD

Quality of Life: AD (Interview Version for the person with dementia)				
Interviewer administer according to standard instructions. Circle responses.				
1. Physical health.	Poor	Fair	Good	Excellent
2. Energy.	Poor	Fair	Good	Excellent
3. Mood.	Poor	Fair	Good	Excellent
4. Living situation.	Poor	Fair	Good	Excellent
5. Memory.	Poor	Fair	Good	Excellent
6. Family.	Poor	Fair	Good	Excellent
7. Marriage.	Poor	Fair	Good	Excellent
8. Friends.	Poor	Fair	Good	Excellent
9. Self as a whole.	Poor	Fair	Good	Excellent
10. Ability to do chores around the house.	Poor	Fair	Good	Excellent
11. Ability to do things for fun.	Poor	Fair	Good	Excellent
12. Money.	Poor	Fair	Good	Excellent
13. Life as a whole.	Poor	Fair	Good	Excellent

Comments: _____

Quality of Life: AD

(Questionnaire Version for the Family Member or Caregiver)

The following questions are about your relative's quality of life.

When you think about your relative's life, there are different aspects, some of which are listed below. Please think about each item, and rate your relative's current quality of life in each area using one of four words: **poor, fair, good, or excellent**. Please rate these items based on your relative's life at the **present time** (e.g. within the past few weeks). If you have questions about any item, please ask the person who gave you this form for assistance.

Circle your responses.

1. Physical health.	Poor	Fair	Good	Excellent
2. Energy.	Poor	Fair	Good	Excellent
3. Mood.	Poor	Fair	Good	Excellent
4. Living situation.	Poor	Fair	Good	Excellent
5. Memory.	Poor	Fair	Good	Excellent
6. Family.	Poor	Fair	Good	Excellent
7. Marriage.	Poor	Fair	Good	Excellent
8. Friends.	Poor	Fair	Good	Excellent
9. Self as a whole.	Poor	Fair	Good	Excellent
10. Ability to do chores around the house.	Poor	Fair	Good	Excellent
11. Ability to do things for fun.	Poor	Fair	Good	Excellent
12. Money.	Poor	Fair	Good	Excellent
13. Life as a whole.	Poor	Fair	Good	Excellent

Comments: _____

Appendix H. Outcome measures-Psychometric properties of the scales used in the observational study.

<u>Domain (Sub-domain)</u>	<u>Test(s)</u>	<u>Items</u>	<u>More Information</u>	<u>Type</u>	<u>Time (Mins)</u>
Affect (Depression)*	GDS-30 ¹¹⁰	30-items	Yes/No responses. It is validated against CES-D, CSDD, HAM-D, BDI, and ZUNG ³⁵⁹ . The score of 0–9 signifies no depression; score of 10–19 suggests presence of mild depression; and score of 20–30 suggests severe depression. No moderate level is suggested. It has high internal consistency (alpha), ranging from 0.82 and 0.94. It has a high test-re-test reliability over intervals of 1 week to 2 months ($r=0.80$ to 0.98). It is shown that individual item analysis has good consistency for high functioning but not for low functioning individuals ($\kappa=0.59$) ³²⁶ . Inter-rater reliability coefficients were high with the adapted version ($\text{Kappa}=0.84$) ³⁶⁰ ; and 0.94 (intra-class) and 0.99 (Cohen's Kappa) with short version in Asian population ³⁶¹ ; however, none has been reported for the full version.	Administered (Patient)	5-10 min
	GDSIF-30 ³⁰⁵	30-items	Yes/No responses. The scale is validated against various versions of GDS ³⁰⁵ . It has sensitivity of 0.60 and specificity of 0.67 with a cutoff of >9 ³⁰⁵ .	Administered (Informant)	5-10 min
	HDS-OA ²⁸³	16-items	Yes/No responses. Satisfactory to	Administered (Patient)	5 min

<u>Domain (Sub-domain)</u>	<u>Test(s)</u>	<u>Items</u>	<u>More Information</u>	<u>Type</u>	<u>Time (Mins)</u>
			excellent psychometric properties. Its psychometric properties are examined in 50 older adults (age ranging from 63 to 93) and showed satisfactory internal consistency (alpha= 0.88), strong convergent validity (GDS: r=0.89; GDS-15: r=0.86); a significant difference between depressed and non-depressed groups; high sensitivity and specificity ²⁸⁴ . Also it is validated against BDI-II (r=0.92), and cutoff scores are reported by the author in an abstract presentation ¹¹¹ .		
Neuropsychiatric symptoms (Depression and other symptoms)	NPI ³⁶²	12 area	It has 10 behavioral and 2 neurovegetative areas. Assesses the presence of psychopathology (frequency, severity, and distress). High internal consistency (alpha 0.88), validated in Chinese, islanders, and for nursing home residents. Inter-rater reliability ranging from 93.6% to 100%, depending on the sub-domain, and very high test-retest reliability (r(20) = .79) ³⁰⁶ .	Administered (Informed caregiver)	10-15 min
Cognition (Global)	MoCA ²⁸⁶	8- items	Trails; Cube copy; Clock draw; Naming; Five-item word list; Digit span; Repetition; Verbal fluency; Similarities; & Orientation. High sensitivity and specificity for detecting MCI.	Administered (Patient & caregiver reports)	10-15 min
Quality of life	QOL-	13-	Rated on a 4-point	Administered in	10 min

<u>Domain (Sub-domain)</u>	<u>Test(s)</u>	<u>Items</u>	<u>More Information</u>	<u>Type</u>	<u>Time (Mins)</u>
(Quality of life)	AD ³⁶³	items	scale, with 1 being poor and 4 being excellent. Minimum score is 13 and maximum is 52. Patient's score is weighted higher. Good internal consistency, acceptable validity. has good criterion concurrent validity, excellent interrater reliability with all Cohen's kappa value>0.70, and excellent internal consistency (Cronbach's alpha 0.82) ³¹⁰	Interview (Patient and the caregiver)	

Note: *DSM-IV based. MoCA: The Montreal Cognitive Assessment; NPI:

Neuropsychiatric Inventory; HDS-OA: Hubley Depression Scale for Older Adults; QOL-

AD: Quality of Life-Alzheimer Disease; MoCA: The Montreal Cognitive Assessment;

GDS-30: Geriatric Depression Scale- 30-item; GDSIF-30: Geriatric Depression Scale for

Informant- 30-item.

Appendix I. Feasibility assessment of the proposed study (prevalence of depression for UBCH-CARD)

Multiple feasibility assessment studies were carried out based on clinic attendees with AD between January 2010 to June 2011 with the purpose of gathering data on the presence of signs and symptoms of depression. Relevant data were gathered from patients' charts and from ongoing/past research projects at the UBCH-CARD. This review reveals that diagnosis of depression by DSM criteria is exceedingly rare in AD. Just over 10% of the attending patients during that period were identified to have some depressive symptom(s). These patients were not formally diagnosed with depression. About half of them had a visit with a psychiatrist for tentative depression or other reasons and most were diagnosed with depressive disorders. Currently at the clinic, the number of referred patients visited by a geriatric psychiatrist per month is low, given the limited availability of this professional. Further analysis revealed that at the UBCH-CARD the rate of enrollment of AD patients for research ranged from 25 to 75%. Of the 492 patients invited for research participation, 321 consented, which also included 201 dementia patients. Refer to Table 21-23 for detailed reports of the analyses.

Table 20. Prevalence of depression for UBCH-CARD as per DSM criteria and Meds.

DX	AD
Last year*	385
Cases-depression**	10
Meds.***	39
Overall	1191

Note: duplicates in dataset (several visits); 1191 may not be representative of the number of patients but rather number of visits, which includes 253 dementia no diagnosis.

*For the last year January 2010 to June 2011

**Depression cases were defined as per either diagnosis by clinical impression, symptom positive as per DSM criteria (checklist), neurological impression on affect, and history of depression with current antidepressant treatment. Affect variability or good was reported under neurological examination, and there were several cases of DSM criteria with no MDD diagnosis or visit with geriatric psychiatrist

***Meds were Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, and Venlafaxine, either with diagnosis of depression or not

Table 21. Prevalence of depression for UBCH-CARD expanded on depression and antidepressant

DX	AD
Last year (cases) [Jan 2010-Jun 2011]	10+39
Non-medicated	3
Meds.	36 (92%)
Citalopram (Celexa)	17 (47%)
S-citalopram (Escitalopram)	5 (14%)
Fluoxetine (Prozac)	2 (6%)
Paroxetine (Paxil)	1 (3%)
Sertraline (Zoloft)	3 (8%)
Venlafaxine (Effexor)	3 (8%)
Other	4 (11%)
(bupropion, mirtazapine, trazodone)	
Multiple antidepressant	4 (11%)
Neurological rating (Affect flat=1)	11 (28%)
DSM criteria used (# of cases)	12 (31%)
No-depression	9 (23%)
Yes-depression	3 (8%)
Visit with psychiatrist	16 (41%)
Other than depression*	2 (5%)

Note: Examination date Friday, January 07, 2012. *Other than depression: included agitation, anxiety, apathy; depression category included dysthymia, euthymic, secondary depression. For AD, venlafaxine was additionally used concurrently with other antidepressants (n=2); same for paroxetine (n=1), and other (n=1). For CIND, trazodone was the most used compound in poly-pharmacy (n=2); and then sertraline (n=1). Percent medication for AD group was calculated based on the number of medicated patients (n=36), and percent use of diagnostic approach was based on overall (medicated and non-medicated) (n=39).

Table 22. Percent agreement to participate in other observational studies at UBCH-CARD

<i>RA/ Coordinators</i>	<i>Project</i>	<i>Duration</i>	<i>Patients</i>	<i>Screened</i>	<i>Invited</i>	<i>Stayed</i>
WW	Music therapy (Ongoing)	3 months	AD	58	16	12 (75%)
	OPAR	7 months	AD	About 90% of all patients who have had an appointment at the clinic since we first started recruiting	52	13 (25%)
PS	CLIMAT (Ongoing)	Since 2009	Mild to moderate AD	Charts flagged, there were 6.5% contacted for research,	68% agreed to participate.	33% enrolled.

Table 23. Feasibility reports on number of patients who gave consent for data collection / willingness to be contacted for research at the UBCH-CARD, based on database analysis (JM).

Sept 2011 to Feb 2012	Data Consent	CSF Consent	Blood Consent	Autopsy Consent		
Agreed	321	14	265	5		
Incomplete	33		4			
No Consent	2					
Refused	17	1	4			
(blank)	119	477	219	487		
# of Patients	492					
# of Visits	578					
Data Consent						
DX	Agreed	Incomplete	No Consent	Refused	(Blank)	Grand Total
CIND	78	12		1	28	119
DEM	201	16	2	15	64	298
NCI	1				1	2
(Blank)	41	5		1	26	73
Grand Total	321	33	2	17	119	492

Appendix J. DSM-IV-TR depression criteria

Major Depressive Disorder (MDD)

Single Episode

A. Presence of a single Major Depressive Episode

B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

Note: This exclusion does not apply if all the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of a general medical condition.

Recurrent

A. Presence of two or more Major Depressive Episodes.

Note: To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.

B. The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

Note: This exclusion does not apply if all the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects or a general medical condition.

Specify (for current or most recent episode): Severity/Psychotic/Remission

Specifiers: Chronic; With Catatonic Features; With Atypical Features; With Postpartum

Onset

Specify Longitudinal Course Specifiers (With and Without Inter-episode Recovery) With Seasonal Pattern

Major Depressive Episode (MDE)

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

Note: In children and adolescents, can be irritable mood.

(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by

others)

(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

Note: In children, consider failure to make expected weight gains.

(4) Insomnia or hypersomnia nearly every day

(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) Fatigue or loss of energy nearly every day

(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Minor Depressive Disorder (MiDD)

Also known as minor depression, is a mood disorder that does not meet all criteria for major depressive disorder but in which at least two depressive symptoms are present for two weeks⁵. It is given in the DSM-IV-TR as an example of a Depressive Disorder Not Otherwise Specified.

Appendix K. Item overlap between PDC and HDS-OA

Items	Dep. Mood (sad/hopeless/ discouraged/ tearful)	Dec. positive affect/pleasure (social contacts/ activities)	Social isolation/ withdrawal	Disruption in appetite	Disruption in sleep	Psychomotor changes (eg. Agitation/ retardation)	Irritability	Fatigue or loss of energy	Feelings of worthlessness/ hopelessness/ guilt	Thoughts of death, suicide, plan or attempt
1. Felt useful and needed									X	
2. Noticed changes in appetite				X						
3. Felt full of energy								X		
4. Often felt sad and downhearted	X									
5. Sleeping patterns changed					X					
6. Difficulty concentrating										
7. Interested in usual activities		X	X							
8. Felt that you/others better off if dead									X	X
9. Become irritated more easily than usual							X			
10. Felt different than you usually do(restless/slow motion?)						X	X ²	X ³		
11. Others claim don't look/seem usual self							X ²	X ³		
12. Enjoyed doing things as much as ever		X	X							
13. Felt like everything was your fault									X	
14. Frequently felt like crying	X									
15. Found it harder than usual to make decisions						X ¹				
16. Thought the future looks hopeless	X								X	X ⁴

Note: x¹ (if due to slowing of thought); X²(if irritable); X³ (if fatigue); X⁴ (if associated with suicidal thoughts).

Appendix L. Item overlaps between PDC and GDS-30 or GDSIF-30

Items	dep. Mood (sad/ hopeless/ discouraged /tearful)	dec. positive affect/pleasure (social contacts/ activities)	Social isolation/ withdrawal	psychomotor changes (eg. Agitation/ retardation)	Irritability	Fatigue or loss of energy	Feelings of worthlessness /hopelessness/ guilt	Thoughts of death, suicide, plan or attempt
1. Life satisfaction		x						
2. Dropped activities/interests		x	x					
3. Feel like life is empty	x							
4. Get bored often		x						
5. Hopeful about future	x						x	
6. Bothered by thoughts (can't get out of head)								x ¹
7. In good spirits most of time		x						
8. Afraid something bad will happen to you								x ²
9. Feel happy most of the time		x						
10. Often feel helpless	x						x	
11. Often get restless or fidgety				x				
12. Prefer to stay home rather than go out/do things		x	x					
13. Frequently worry about future								x ³
14. Feel have more memory problems than most								
15. Feel wonderful to be alive now		x						
16. Feel downhearted and blue	x							
17. Feel worthless the way are now	x						x	
18. Worry a lot about the past								
19. Find life very exciting		x						
20. Hard to get started on new projects			x					
21. Feel full of energy						x		
22. Feel situation is hopeless	x						x	
23. Think most people are better off	x							
24. Frequently get upset over little things	x				x			
25. Frequently feel like crying	x							
26. Have trouble concentrating								
27. Enjoy getting up in the morning		x						
28. Prefer to avoid social occasions		x	x					
29. Easy to make decisions				x*				
30. Mind clear as it should be				x*				

Note: Disruption in Appetite and Sleep items were not on GDS-30 or GDSIF-30; therefore, they are dropped from this table. X*(if due to slowing of thought); X¹ (if suicidal thoughts), X²(if death due to suicide), X³ (if worried about suicide).

Appendix M: Survey: Content Validity of a Depression Scale

Please circle Yes OR No or tick the appropriate box and make comments when applicable for the following questions. The completed survey can be either scanned and then emailed back to the sender [.....@.....], or be faxed to the attention of Amir A. Sepehry at xxx-xxx-xxxx.

Demographics:

Age:

Specialty:

Gender:

In practice/research/both:

Title:

Location
(country/city):

Number of years in
practice/research since
graduation

Years of experience
working:

a) With depression

c) With Alzheimer's disease
specifically

b) With elderly

Questions regarding the scale:

Q1. Is the scale's name "Geriatric Depression Scale" appropriate for use with PDC-dAD?

Yes ☐ No ☐

If no, please suggest an alternative name:

Q2. The GDS has 30 items. If used to screen for depression in Alzheimer's Disease patients, how would you describe the length of the GDS?

Too short OR About right OR Too long

Please explain your choice:

Q3. Is the instrument directive [below] easy to understand for Alzheimer patients of different levels of cognitive impairment?

“Please read each question and select the best answer that describes how you’ve been feeling in the past **week**.”

- | | |
|--------------------|---------------|
| 1- Not at all easy | 3- Quite easy |
| 2- Somewhat easy | 4- Very easy |

Levels of Cognitive Impairment in AD	1	2	3	4
Mild cognitive impairment				
Moderate cognitive impairment				
Severe cognitive impairment				

Q4. How easy do you think the ‘yes/no’ response format of the GDS is for Alzheimer patients of different levels of cognitive impairment to use? Please check your response.

- | | |
|--------------------|---------------|
| 1- Not at all easy | 3- Quite easy |
| 2- Somewhat easy | 4- Very easy |

Levels of Cognitive Impairment in AD	1	2	3	4
Mild cognitive impairment				
Moderate cognitive impairment				
Severe cognitive impairment				

Q5.1. Is a self-report approach (in which the **patient** reads and responds to the GDS) appropriate for Alzheimer patients of different levels of cognitive impairment?

- | | |
|---------------------------|----------------------|
| 1- Not at all appropriate | 3- Quite appropriate |
| 2- Somewhat appropriate | 4- Very appropriate |

Levels of Cognitive Impairment in AD	1	2	3	4
Mild cognitive impairment				
Moderate cognitive impairment				
Severe cognitive impairment				

Q.5.2. Is an administrator-read approach (in which an **administrator** reads GDS items and records the patient's answer) appropriate for Alzheimer patients of different levels of cognitive impairment?

- | | |
|---------------------------|----------------------|
| 1- Not at all appropriate | 3- Quite appropriate |
| 2- Somewhat appropriate | 4- Very appropriate |

Levels of Cognitive Impairment in AD	1	2	3	4
Mild cognitive impairment				
Moderate cognitive impairment				
Severe cognitive impairment				

-----Continue to next page-----

Q6. For the next section, based on the provided rating scale, please assign the level of relevance of the GDS items for NIMH-PDC-dAD [Please refer to the list of symptoms provided in Olin et al. 2003; also in the appendix].

- 1- Not relevant 3- Quite relevant
2- Somewhat relevant 4- Highly relevant

Items	1	2	3	4
1. Are you basically satisfied with your life?				
2. Have you dropped many of your activities and interests?				
3. Do you feel that your life is empty?				
4. Do you often get bored?				
5. Are you hopeful about the future?				
6. Are you bothered by thoughts you can't get out of your head?				
7. Are you in good spirits most of the time?				
8. Are you afraid that something bad is going to happen to you?				
9. Do you feel happy most of the time?				
10. Do you often feel helpless?				
11. Do you often get restless and fidgety?				
12. Do you prefer to stay at home rather than go out and do things?				
13. Do you frequently worry about the future?				
14. Do you feel you have more problems with memory than most?				
15. Do you think it is wonderful to be alive now?				
16. Do you feel downhearted and blue?				
17. Do you feel pretty worthless the way you are now?				
18. Do you worry a lot about the past?				
19. Do you find life very exciting?				
20. Is it hard for you to get started on new projects?				
21. Do you feel full of energy?				
22. Do you feel that your situation is hopeless?				
23. Do you think that most people are better off than you are?				
24. Do you frequently get upset over little things?				
25. Do you frequently feel like crying?				
26. Do you have trouble concentrating?				
27. Do you enjoy getting up in the morning?				
28. Do you prefer to avoid social occasions?				
29. Is it easy for you to make decisions?				
30. Is your mind as clear as it used to be?				

Please double-check that you haven't missed any items above.

Q7. Have all of the relevant symptoms from the NIMH-PDC-dAD been included in the GDS?

Yes ☐ No ☐

If no, which symptom(s) are missing:

Q8. Are there any additional symptoms or items that you think should be included to screen for depression in Alzheimer's Disease?

Yes ☐ No ☐

If yes, please list and explain:

Q9. Are there any items that you think should be removed from the GDS when screening for depression in Alzheimer's Disease?

Yes ☐ No ☐

If yes, please list and explain:

Q10. Do we need to add, "Please explain", for any GDS items?

Yes ☐ No ☐

If yes, which items need further explanation from the respondent?

Q11. Is there anything else about the GDS that you would like to tell us when using it to screen for depression in Alzheimer's Disease?

Yes ☐ No ☐

If yes, please explain:

-----The End-----

Appendix N: Published article leading to this thesis [Sepehry et al. Drugs and Aging (2012) PMID: 23079957]

[Effect of SSRIs in Alzheimer Disease with comorbid depression:
A meta-analysis of depression and cognitive outcomes](#)

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