

Dependence as a unifying construct in defining Alzheimer's disease severity

Trent McLaughlin^a, Howard Feldman^b, Howard Fillit^c, Mary Sano^d, Frederick Schmitt^e, Paul Aisen^f, Christopher Leibman^{a,*}, Lisa Mucha^g, J. Michael Ryan^g, Sean D. Sullivan^h, D. Eldon Spackmanⁱ, Peter J. Neumann^j, Joshua Cohen^j, Yaakov Stern^k

^aJanssen Alzheimer Immunotherapy Research & Development, South San Francisco, CA, USA

^bDivision of Neurology, University of British Columbia, Vancouver, BC, Canada; Neuroscience Global Clinical Research, Bristol-Myers Squibb, Wallingford CT, USA; and Department of Neurology, Yale University, New Haven, CT, USA

^cDepartment of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY, USA

^dMount Sinai School of Medicine, New York, NY, USA

^eSanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

^fDepartment of Neurosciences, University of California, San Diego, San Diego, CA, USA

^gPfizer Inc., Collegeville, PA, USA

^hDepartment of Pharmacy, University of Washington, Seattle, WA, USA

ⁱCentre for Health Economics, University of York, York, United Kingdom

^jCenter for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA

^kTaub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA

Abstract

This article reviews measures of Alzheimer's disease (AD) progression in relation to patient dependence and offers a unifying conceptual framework for dependence in AD. Clinicians typically characterize AD by symptomatic impairments in three domains: cognition, function, and behavior. From a patient's perspective, changes in these domains, individually and in concert, ultimately lead to increased dependence and loss of autonomy. Examples of dependence in AD range from a need for reminders (early AD) to requiring safety supervision and assistance with basic functions (late AD). Published literature has focused on the clinical domains as somewhat separate constructs and has given limited attention to the concept of patient dependence as a descriptor of AD progression. This article presents the concept of dependence on others for care needs as a potential method for translating the effect of changes in cognition, function, and behavior into a more holistic, transparent description of AD progression.

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Alzheimer's disease; Dementia; Functional impairment; Dependence; Disease progression

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disorder characterized by loss of memory and cognition, declining ability to perform activities of daily living (ADL), changes in personality and behavior, and increased use of health care resources and medical services. An estimated 27 million persons worldwide are currently living with AD; this number

is expected to quadruple to more than 106 million by 2050, with 1 in 85 persons living with the disease [1,2]. In addition, AD places a considerable economic burden on the families of patients and on society. In the United States alone, AD is estimated to cost approximately \$80 billion per year, making it this country's third most costly disease [3].

AD can be described in a variety of ways. Clinicians tend to focus on cognition, function, or behavior in their descriptions (with each specialty selecting its preferred construct and measurement). The cognitive feature that is most commonly associated with the disease is memory impairment, although decision-making, judgment, spatial

*Corresponding author. Tel.: 650-794-2534; Fax: 650-794-2504.

E-mail address: cleibman@janimm.com.

orientation, thinking/reasoning, and verbal communication might also be affected. Functional impairment in AD is typically referred to as disability in everyday functioning that results primarily from cognitive impairment, with notable losses in the ability to perform ADL. In addition, changes in personality and behavior are also common in patients with AD and might include aggression, wandering, apathy, and motor restlessness. These changes can be socially disruptive, can create high levels of caregiver stress and burden, and can also affect a patient's ability to perform ADL [4].

Few attempts have been made to integrate and model the domains of cognition, function, and behavior [5,6]. Earlier attempts to describe the progression of AD have focused primarily on discrete measures of cognitive function [7]. Although changes in cognition are the hallmark of dementia, especially in early disease, they are not the only symptom and, from an economic perspective, are not the sole drivers of the use of resources such as caregiver time, medical care, and nursing home placement [8].

Furthermore, as noted by Loveman et al [9], the literature provides limited and conflicting information on typical AD progression pathways in each of the three domains, and the variety of discrete measures that are used to describe disease-associated changes might further complicate models of progression. In addition, the method used to track the progression of AD might affect how patients are treated during the course of the disease and whether the treatments are viewed as successful [10]. For example, after attempting appropriate care of an AD patient who is repetitive and agitated, clinicians might opt to prescribe a medication that causes sedation. If this intervention is assessed strictly on the basis of agitation, it might be considered a success, even though the lives of both the patient and caregiver might now be less rewarding [11]. Because patients often experience different levels of disrupted behavior during the course of AD, the challenge is to manage behavioral decline without adversely affecting the functional and cognitive abilities of the patient at the time of the behavioral disturbances [10]. Tracking the progression of AD by focusing on a single aspect of the disease (eg, behavior) might mean that other important aspects (eg, function, cognition) might not be sufficiently addressed. A broader measure or concept of the overall impact of AD progression would address this issue by reflecting at least some of the negative effects of pharmacologic treatment as well as the positive outcomes.

A broader measurement of AD progression would also better integrate the concerns of individuals who are directly affected by the disease, specifically the patients and their loved ones. Although cognitive test scores provide clinicians with quantitative measures of memory and other mental functions, persons with AD might be more concerned with the overall effect of the disease than with its impact on individual domains [12,13]. Likewise, individuals who are concerned with resource allocation and health care costs tend to measure AD progression in terms of the patient's direct health care

costs as well as living arrangements (eg, home versus an assisted living facility versus a nursing facility); living arrangements are easily assessed, and costs can be easily differentiated across locations. However, a patient's living situation is a function of multiple factors that might or might not be related to the severity of AD. As a result, living environments do not provide a transparent, meaningful description of the overall impact of the disease for patients, caregivers, or clinicians. Although alternative measures of caregiver burden, such as the Zarit Burden Interview [14], provide a broad indicator of the effect of caregiving, these tools do not explicitly measure changes in patient disease severity in a transparent manner. In other words, a useful measure of AD progression must not only be broad, but it must also convey the effect of AD progression in a way that is meaningful to multiple audiences.

We propose in this article that dependence, or the level of assistance required by a patient with AD, should be used as a construct for assessing the effect of AD treatment. Its correlate, independence, is an attractive measure for assessing disease progression because it has been shown to decline over time [15], is associated with other domains such as cognition and/or function [16], and is easily assessed/measured during both short and long periods. Similarly, a patient's level of dependence logically is related (directly and indirectly) to the degree of impairment in the individual domains of cognition, function, and behavior as well as to other factors that limit a patient's abilities. Mapping of AD progression as stages of increasing dependence on others would provide patients, families, and other decision makers with a better idea of current and future service needs and help quantify the impact of any treatments intended to delay this progression.

Describing AD progression as a process of increasing dependence on others would not replace current (or future) clinical measures (cognitive, functional, behavioral), but instead it would be a complementary measure that would allow translation of those end points into a common language for non-clinical audiences to use when they assess the impact of AD and the potential benefits of interventions. Thus, it might be beneficial to include a measure of dependence alongside clinical end points in clinical trials, descriptive studies, registries, and other types of studies that explore AD and the effect of its treatment. Furthermore, continued discussion of such a concept in the scientific literature would be of value to clinicians who are not currently involved in clinical trials but are responsible for the day-to-day care of AD patients and their loved ones.

The remainder of this article discusses the concept of dependence and reviews the literature on the subject as an initial attempt to explore the usefulness of characterizing AD progression in terms of increasing dependence.

Promoting independence or avoiding increased dependence previously has been highlighted as a worthy goal for the field of dementia care [17]. However, the multiplicity of terms, tools, and operational definitions used to describe and measure dependence has limited the construct's

effectiveness as a measure of both AD progression and therapeutic impact.

If dependence is to be accepted as a measure of the impact of AD progression, some degree of consensus must be reached on the appropriate terminology and on its relationship to other constructs, its operational definition, and the instruments used to measure it. For example, dependence, as a construct, should reflect the level of assistance needed by a patient, not necessarily the level of assistance that is provided. Dependence differs from measures of care service (eg, the amount of caregiver time provided), which reflect not only patient need but also constraints on supply (eg, amount of caregiver time available, availability of care facilities, and patient and family financial resources). In this article, dependence is defined as the amount of care required from others (according to text from the Dependence Scale [16]). This definition was selected over a dichotomous measure (eg, independent versus dependent [18]) because focusing on overall care needs allows for translation of multiple facets of the disease into a single measure, and using a scale with multiple levels provides more granularity for measuring changes over time. Our primary objective was to review the current literature on dependence to establish a consensus on and recommendations for incorporating dependence into AD therapeutic and outcomes research. We describe the concept of dependence in AD and its relationship to other commonly used AD domains/measures (ie, cognition, function, and behavior).

2. Dependence: Conceptual framework

Dependence in AD can be characterized as the measurable impact of changes in cognition, function, and behavior that result in an increased need for assistance. Although these domains measure different aspects of the impact of AD, they have an inter-related and aggregate effect (Fig. 1). Cognitive deficits are initially subtle/mild effects that might require patients to seek assistance with social activities (this need for assistance might correspond to limitations in handling community affairs and home and hobbies as measured on the Clinical Dementia Rating scale [19]). Over time, cognitive deficits might lead to increased reliance on others for coping with memory-related impairments (eg, keeping appointments), disorientation (including maintaining proper temporal/spatial orientation), executive impairments that lessen the patient's ability to manage finances or medications, and finally, apraxia (ie, difficulty executing complex coordinated movements), which might be associated with memory, judgment and problem solving, and orientation categories on the Clinical Dementia Rating [19]. Functional impairment, which is operationally defined as a patient's inability to perform specific activities, directly translates to dependence on others and to the loss of functional autonomy. When patients with AD can no longer dress themselves, they will be dependent on caregivers to complete parts of their everyday routines. The behavioral sequelae of AD vary but might

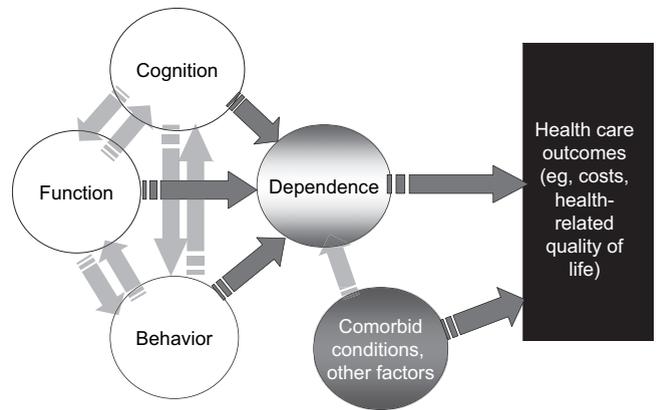


Fig. 1. Dependence: Conceptual framework.

include changes such as apathy, irritability, depression, anxiety, restlessness, agitation, and aggression. For example, wandering often leads to increased personal risk of injury and the need for management strategies that involve the extended caregiving community. Although behavioral symptoms vary among individuals, they might generally lead to increased assistance needs (eg, supervision to minimize harm to the patient or, possibly, other individuals). For example, Murman et al [20] found that neuropsychiatric symptoms, as measured by the Neuropsychiatric Inventory, were significantly correlated with a measure of dependence (the Dependence Scale), with changes in the Neuropsychiatric Inventory score accounting for 22% of the variation in dependence level.

Dependence can also be depicted to share a temporal relationship with changes in cognition, function, and behavior. As Fig. 2 illustrates, the relative contributions of cognitive, functional, and behavioral impairments on the overall level of dependence would be expected to change over time, as the disease progresses and as the relationship between the patient and his or her environment changes. For example, in early AD/mild cognitive impairment, changes in cognition (eg, the patient becomes forgetful and/or confused in social situations) might be the primary contributor to changes in

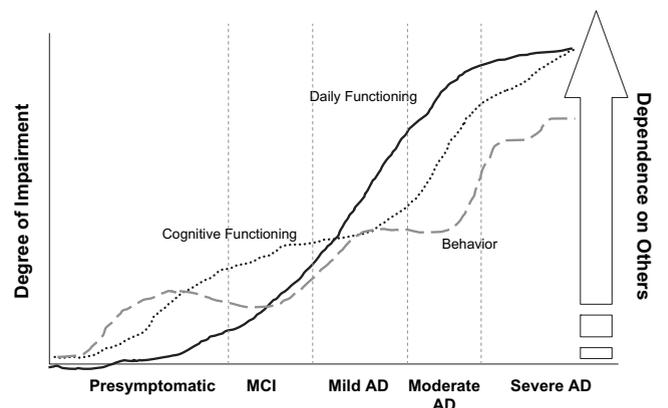


Fig. 2. Impacts of impairments in cognition, function, and behavior on patient dependence on others.

the level of dependence. Functional impairment (eg, related to driving, financial management) would make only a minimal contribution to increased dependence in the early stages but would be expected to play a larger role with the passage of time and disease progression. Behavioral issues, on the other hand, tend to be more difficult to predict; even patients with mild cognitive impairment might experience depression, apathy, or anxiety, which might make patients more difficult to care for and might lead to a decrease in their ability to care for themselves and therefore to increased dependence on others. In all cases, the trend is toward greater dependence on others, whether it is primarily caused by changes in cognition, function, or behavior.

It should be noted that a person's level of dependence might be further influenced by factors other than those related to AD severity. For example, comorbid conditions, physical handicaps, or environmental factors might play an important role in defining an overall level of dependence on others for care needs. However, the primary focus of this article is to explore the concept of dependence as it relates to AD, ie, how the definition of dependence could be operationalized to focus primarily on the relationship between changes in AD symptomatology and changes in patient reliance on others for care needs. Furthermore, for the purpose of this discussion, dependence is considered to be a separate construct from disability; the latter is a broader measure of the general health and well-being of a person beyond merely his or her AD symptomatology/severity.

Previous attempts to characterize dependence either have focused on function or have defined a small number of discrete stages (eg, independent versus dependent), whereas the dependence framework described herein has the advantage of being able to characterize the complete range of the disease's impact and severity. Because the transition from completely independent to completely dependent occurs on a continuum, measures of dependence should not be characterized as a dichotomous quantity or as an arbitrarily limited number of discrete levels, as has been the case with previous measures [15,18,21–23]. Furthermore, when changes in cognition, function, and behavior are translated into a single overall measure of disease impact, patients, caregivers, and providers might gain a clearer understanding of the typical course of the disease.

3. Discussion of independence/dependence in the literature

The idea of associating AD with the loss of independence is not new. A number of researchers have described AD progression in this way. For example, Bullock and Hammond [24] described the natural course of AD as a gradual loss of independence, dividing it into four stages: mild (patient has cognitive deficits that might necessitate retirement from work, but he or she remains capable of living independently); moderate (need for assistance with ADL and personality changes mean that the patient might not be able to safely

live alone); severe (patient has lost the ability to ambulate independently and can no longer eat without assistance); and for patients who live long enough, terminal, which is characterized by the inability to walk (even with assistance) or to communicate with others [24]. Much of this description comes from an earlier article by Volicer [25], who presented a similar description of progressive dementia.

Barbas and Wilde [26] reviewed the impact of dementia from a legal perspective and noted that the loss of competency, which typically occurs as the disease progresses beyond the early stages, creates unique challenges and interferes with a patient's ability to live independently. Finally, Woods [17] dedicated an entire article to the need for promoting well-being and independence among people with dementia and noted the lack of methods for measuring these traits in this population.

Although articles identifying loss of independence as an important feature of AD have been in the public domain for many years, the lack of a concise operational definition of dependence, as well as the lack of a specific measurement approach, has likely limited the attention that has been given to this concept. The next section provides an overview of instruments that have been developed to measure changes in dependence in patients with AD.

3.1. Broad measures of dependence: Published instruments

A MEDLINE search of all indexed journals published in English from 1980 through 2008 was conducted by using the terms *dementia*, *Alzheimer's disease*, *dependence*, and *independence*. This initial query identified 521 potentially relevant articles containing these search terms. After excluding articles focused on alcohol or drug dependence and those that included the search terms in a way that was unrelated to the current review (eg, context dependent, pH dependent, independent variable), a working set of 98 articles remained.

Articles related to purely functional measures (eg, measured only ADL) were then excluded ($n = 41$, see Appendix), as were measures of subjective caregiver burden (eg, Zarit Burden Interview, $n = 10$; see Appendix), to focus primarily on instruments purported to measure the level of patient dependence on others for care needs.

Of the remaining 47 articles that discussed dependence/independence and dementia, a semistructured review of abstracts was conducted to further exclude articles that did not discuss specific instruments or research activities ($n = 29$; see Appendix), which left 18 articles that described some measure of dependence in dementia or AD.

The reference lists from articles obtained through the MEDLINE search were also reviewed for pertinent sources. This literature search indicated that relatively few instruments have been developed to measure dependence in patients with AD (Table 1) [15,16,18,27–34].

The Record of Independent Living (RIL) is a 37-item instrument designed to evaluate cognitive decline in elderly

Table 1
Instruments for measuring degree of dependence

Instrument	Target population	Administration	No. of items	Comment	Reference citation(s)
RIL	Patients with mild to severe dementia and behavioral problems	Informant-completed	37	Beyond the original publication, there is limited information available on use of this instrument	Weintraub [27]
ILS	Patients with mild to severe dementia	Clinician-administered to patient	70	Includes several subscales such as tests of cognition and problem-solving behaviors	Loeb [28], Martin-Cook et al [29], Revheim and Medalia [30]
BGP	Patients with moderate to severe dementia, institutional setting	Nurse rating of patient	35 (BGP-dependency: 23 items)	Primary focus is behavioral issues and how they relate to care needs in nursing home patients	Van der Kam et al [31], Van de Winckel et al [32]
NCD scale	Nursing home patients with dementia or learning disabilities	Nurse rating	15	Assesses 15 features of care dependency in patients residing in nursing homes	Dijkstra et al [35–37]
DS	Patients with mild to severe dementia in a community or institutional setting	Informant-completed	13	Knowledgeable informant estimates amount of care needed, not necessarily the amount of care that is provided	Brickman et al [15], Caro et al [18], Holtzer et al [33], Sarazin et al [34], Stern et al [16]

patients [27]. The RIL has three sections (activities, communication, and behavior) and was designed to rectify the potentially excessive focus of other instruments on ADL. An exclusive focus on loss of the ability to perform ADL can be misleading because it ignores patients with AD who might have altered mental states that change their conduct, personality, or communication, but who have no physical disabilities. Instruments that essentially ignore these cognitive and behavioral changes might miss some of the earliest signs of a dementing illness [27]. However, acceptance of the RIL in the mainstream literature seems to be limited. In addition, no information is available on changes in RIL item scores over time. Also, the RIL does not provide any indication of hierarchy among items; the RIL does not distinguish complex capabilities (eg, managing one's finances) that AD typically compromises early in the disease process from more basic capabilities (eg, toileting) that typically are affected later on.

The Independent Living Scales (ILS) assessment was designed to provide a broad measure of dependence in patients with dementia by incorporating cognitive/reasoning skills in addition to physical measures [28,30]. The ILS is conducted by a clinician and consists of five subscales and two factor-analyzed subscales. The memory-orientation subscale evaluates an individual's ability to recall a list and recognize an object as well as his or her orientation to time and place. The managing money subscale includes concrete tasks such as monetary calculations. The managing home and transportation subscale assesses an individual's ability to use public transportation and to perform tasks involved in managing a home, such as using a telephone. An individual's awareness of health problems and potential safety hazards, as well as the ability to handle medical emergencies, is assessed on the health and safety

subscale. Finally, attitudes and concerns regarding interpersonal relationships are assessed on the social adjustment subscale. The two factor-analyzed subscales (composed of items from all five aforementioned subscales) are the performance-information subscale and the problem-solving subscale.

The ILS differs from other instruments in that the scales are clinician-driven measures, requiring the patient to perform a number of tests that each take 30 to 45 minutes. To date, the ILS has not been widely used in populations with dementia, possibly because of the time required to administer the scales. Also, it is unclear how disease progression can be measured with the ILS, given the focus on task performance and the limited information on ordering/scoring of tests over time.

The Behavioral Rating Scale for Geriatric Patients (BGP) [31,32] was originally developed in The Netherlands in 1971 as an adaptation of an older scale. The BGP consists of 35 items covering six aspects of patients' behavior as it pertains to care in a nursing home setting: helplessness, aggressive behavior (eg, threatening behaviors such as beating or kicking), physical disability (eg, requirement for assistance with eating, incontinence, the need for restraints or supports to avoid falling), depressive behavior, mental disability (eg, paranoia), and inactivity (eg, daytime drowsiness, lack of involvement in useful activities). The items primarily focus on behaviors that would be problematic from a nursing care/assistance standpoint, such as additional supervision needs as a result of inappropriate behaviors or assistance with basic ADL, and are assessed by an informed respondent, typically a nurse or a family member.

The BGP-dependency subscale, which consists of a subset of the original 35 BGP items, has been used in the study of

memantine in patients with moderately severe to severe AD [38]. Although the terms used to describe the BGP, especially the BGP-dependency subscale, are similar to the language used in this article (eg, care dependency, care needs), the BGP is focused primarily on patient behavior, and given the heavy attention paid to behaviors that are more prevalent in a nursing home situation, it is unlikely that the scale in its current form would be useful for a population with less severe AD.

The Nursing Care Dependency (NCD) scale differs from other measures of dependence in that it was developed on the basis of nursing theory and specifically assesses a patient's degree of reliance on nursing care [35–37]. The NCD is composed of 15 different dimensions of human need: eating and drinking, incontinence, body posture, mobility, day/night pattern, getting dressed and undressed, body temperature, hygiene, avoidance of danger, communication, contact with others, sense of rules and values, daily activities, recreational activities, and learning ability. A nurse who is directly involved in the care of the patient rates the patient's degree of dependence for each of these dimensions. In the short version of the NCD, a 5-point Likert scale is used to rate each dimension. The longer version of the NCD uses five written criteria, describing varying degrees of aid required by a patient, for each dimension of need. The nurse selects the criterion in each dimension that most accurately describes the patient's degree of dependence. By assessing the patient's degree of dependence on nursing care, the NCD allows nurses to better plan individualized patient care.

The primary objective of the Dependence Scale (DS), which is completed by a reliable informant such as a caregiver, is to measure the current level of care required by a patient [16]. The 13 items on the DS range from subtle forms of dependence, such as the need to be watched or accompanied outside, to more gross forms, such as the need for assistance in self-care activities. The instrument is hierarchical in nature, with the items representing increasing levels of assistance. For example, item A addresses the need for simple reminders or advice; item D addresses the ability to independently perform household chores; later items address the need for assistance with moving and tube feeding. Items A and B are scored on a 3-point scale (0 = never, 1 = occasionally, 2 = frequently), items C through M are scored on a 2-point scale (0 = no, 1 = yes). The sum of the scores from the 13 items is used to characterize a patient's overall dependence, which is associated with the patient's living situation and has been correlated with, but is independent of, measures of cognition and function [15].

The DS has been used in a number of observational studies and in trials of AD treatments [15,20,33,34,39–41]. Considerable evidence also supports it as a measure of dependence (as the concept was described earlier), as characterized by deficits in cognition, function, and behavior. In an analysis of patients with AD in the Midwestern United States, Murman et al [20] found that dependence (as measured by the DS) was a statistically significant mediating/explanatory var-

iable between various clinical measures and AD-related costs. In particular, measures of cognition, behavior, and other factors predicted a patient's dependence level, as measured by the DS, which in turn predicted the patient's total AD-related costs, explaining 40% of the variation.

3.2. Dependence and economic evaluations of AD treatments

Attempts to quantify the economic benefits of the treatment of AD with acetylcholinesterase inhibitors or memantine primarily have focused on end points related to cognition and, rarely, function. However, dependence (or independence) has, on occasion, been used in economic evaluations to translate short-term treatment benefits into long-term consequences. For example, in their cost-effectiveness model of memantine in Finland, Francois et al [42] defined health states on the basis of physical dependence, place of residence, and cognitive function. One of the primary findings of this model was that memantine therapy was associated with approximately 4 extra months of independence. Caro et al [18] operationally defined dependent on the basis of two different measures: requirement for >12 hours of supervision or a DS dependence level ≥ 3 . Although this definition allowed for straightforward comparisons of resource use and quality of life for independent versus dependent patients and also allowed for calculation of time until a person was considered dependent, creating a dichotomous variable to describe what should be a continual process (ie, an AD patient typically is not independent one day and dependent the next) limits the utility of this measure for broader applications.

4. Summary

Measures currently used to assess AD treatment efficacy do not meaningfully describe the overall impact of the disease on patients and their loved ones. To provide a more complete picture of AD, assessment measures should incorporate aspects of cognitive, functional, and behavioral impairments and present these factors in a way that multiple audiences can understand.

Previous research indicates that AD is strongly associated with increased dependence (reliance on others for care and basic needs). Dementia is also a risk factor for mortality in a variety of populations [43]. Compared with individuals without AD, those with AD can expect to have shorter lives and spend a greater share of their remaining time dependent on others.

Previous attempts to describe AD progression in economic analyses have partially touched on the idea of dependence as it relates to living situation. For example, in the recent appraisal document from the United Kingdom's National Institute of Clinical Effectiveness (NICE) [44], a review of potential long-term benefits and costs of acetylcholinesterase inhibitor use was conducted by using a model based on patient care requirements, dichotomized

into “not requiring full-time care” or “requiring full-time care.” Although the NICE authors noted that this was a gross oversimplification of AD, they also commented that patient care needs were the most transparent depiction of AD progression for determining economic impact. Therefore, further exploration of patient dependence or care needs with greater granularity might benefit agencies such as the NICE as they continue to evaluate AD therapies.

Further research on the concept of dependence might also provide a more comprehensive, meaningful, and consistent method for characterizing AD progression from the mild through the severe disease stages. Loss of independence, which is gradual during some periods but devastatingly fast at other times, begins early in the course of AD. Unlike many other chronic conditions, AD also affects caregivers and family members in the early stages of the disease, as patients become increasingly reliant on them. Affected individuals lose the ability to perform certain activities, require increased supervision, and eventually can no longer live on their own. This dependence might be an important factor in predicting patient disability, expenses, and caregiver stress throughout the course of the disease. Characterizing typical changes in dependence can help caregivers plan ahead.

Considering the link between patient dependence and the need for additional support or care, a measure of this construct presents a relatively straightforward way of translating clinical changes into units of economic relevance (ie, resource use and/or quality of life). Such a construct would be preferential to those used in previous attempts to model the relationship between cognition and economic consequences, in which the relationship was weak and difficult to describe, or even in multiattribute models, which, because of their complexity, are difficult to interpret and/or communicate. A model based on the concept of increasing dependence would be useful to policy makers and/or economists in that it might increase their confidence that changes in resource use and/or quality of life are indeed due to changes in the measure of AD progression. Such a model would also be useful to other audiences (eg, physicians, patients, caregivers) for which a clear description of the disease path and potential impact of intervention(s) is not currently available.

A potential limitation of using dependence as a measure of AD progression is that the amount of assistance required by a patient might be influenced by non-disease-related factors, including the individual's level of care or dependence at baseline. However, current measures of cognition and function have similar limitations. For example, measures of function that review specific activities (eg, meal preparation) assume a certain level of premorbid functioning that might not be appropriate for all individuals. Similarly, cognitive examinations that incorporate word lists or other memory tests assume a premorbid level of education and/or cognitive ability that might not apply to everyone. For all these measures, change from baseline level is the most important gauge of disease progression. Although individuals might be diag-

nosed with AD at different levels of dependence (or cognition or function), their need for assistance should increase at similar rates as their disease progresses.

Another potential issue relates to who should rate a patient's dependence level. With the exception of the ILS and NCD Scale, most measures of dependence identified in the literature require input from an informant (usually a caregiver). Although a patient's primary caregiver should have the greatest insight into the patient's daily needs, an independent observer would be less likely to be personally affected by the patient's dependence. Congruence between caregiver and/or informant and independent observer assessments of patient dependence has not yet been established.

These limitations primarily relate to how to best operationalize the concept of dependence. All instruments that are currently available and are described in this article have potential limitations. For example, the BGP-Dependency and NCD scales were both developed for use in nursing homes and therefore focus primarily on severe AD. Information on the performance of the ILS and RIL and how scores on these instruments relate to conventional measures of cognition, function, or behavior is sparse or nonexistent; therefore, we cannot recommend either of these instruments for widespread use. More data have been published on the DS, but because this instrument was not developed by using standard psychometric techniques, we are unable to comment on its overall performance. Furthermore, the handling of individual items (eg, scoring of the first two items versus all later items) requires further investigation, as well as the grouping of certain elements into one item (eg, need for reminders with chores, shopping, playing games) and further clarification of the terms used to describe frequency of events (eg, occasionally = once per month, frequently = once per week). Thus, because the DS has the most supporting information, in our opinion it would be considered the most viable candidate of the instruments identified here. However, the DS still requires further investigation before it can be recommended for widespread use.

As evidenced by the paucity of instruments and the limited supporting data for the few available instruments, further developments in the measurement of dependence would be valuable. In particular, the development of a new instrument that incorporates the knowledge gained from the measures described herein, as well as from review of other measures of AD progression, would be a valuable addition to the field. Although it is beyond the scope of this article to develop and/or test a new measure, the available data suggest that a hierarchical scale that encompasses the effect of cognition, function, and behavior during the entire disease course (ie, from early through late-stage disease), allows for measurement of the presence and frequency of symptoms, and is administered with minimal time burden on the clinician or caregiver would be optimal. Scoring should allow for calculation of an overall level of dependence that can be translated into a meaningful description of disease course and should also allow for flexibility and/or granularity around specific symptoms (eg,

acknowledging that different symptoms or even different frequencies of the same symptom can be associated with different levels of dependence and support needs). Evidence to support the linkage between scores on this new scale and conventional measures of cognition or function would be useful in increasing confidence in its content validity.

AD is a devastating illness, not only for patients but also for those around them. The disease can have a variety of effects that might not be adequately reflected by conventional measures of cognition, function, or behavior. Instead, a more comprehensive view of the disease and its impact is needed to more appropriately describe its progression. Dependence (or loss of independence) is a potentially useful concept for describing disease progression in broader terms; decrements in each of the conventional measures can be associated with increased dependence, and the concept of lost independence corresponds to how patients and caregivers typically view the effect of AD. Measures of dependence might help clinicians better understand the health, economic, and pharmacoeconomic impact of AD. Potential measures of the concept of dependence have been suggested in this article. Additional work is needed to refine the concept and to further validate the current measures or develop new ones.

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5. Appendix

5.1. Excluded articles: ADL/functional dependence only

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