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NIA-AA Framework on Alzheimer's Disease: Application to Clinical Trials

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Abstract

INTRODUCTION: The NIA-AA Research Framework on Alzheimer's Disease represents an important advance in the biological characterization of the Alzheimer's disease (AD) spectrum.

METHODS: The NIA-AA Framework is considered as it applies to clinical trials.

RESULTS: Using the combination of amyloid (A), tau (T), and neurodegeneration (N) biomarkers, the Framework provides a means of defining the state of patients with regard to Alzheimer pathologic change. The Framework is relevant to clinical trials of disease-modifying agents allowing participants to be characterized biologically at baseline. The ATN Framework can also inform trial outcomes. The preclinical phase of the disease after amyloid deposition is defined by A+T-N- and the transition to prodromal disease and dementia is characterized by the addition of T and N. Most symptomatic patients in clinical trials are in the class of A+T+N- and A+T+N+.

DISCUSSION: The NIA-AA Framework on Alzheimer's Disease represents progress in providing biomarker profiles of participants in the AD spectrum that can be used to help design clinical trials.

Keywords

Alzheimer's disease; Clinical trials; NIA-AA Framework; biomarkers; disease-modification; amyloid; tau; neurodegeneration

1.0 Introduction

The National Institute on Aging – Alzheimer's Association (NIA-AA) Alzheimer's Diagnostic Framework[1] seeks to define the Alzheimer's spectrum in terms of biomarkers and to distinguish Alzheimer's disease (AD) from non-Alzheimer causes of cognitive impairment by biomarker criteria. The classification uses three types of biomarkers – amyloid (A), tau (T), and neurodegeneration (N). Each of the types of biomarkers has several representatives (Table 1) including cerebrospinal fluid (CSF) measures of amyloid beta-protein 42 ($A\beta_{42}$) and amyloid imaging for A; CSF phospho-tau (p-tau) and tau

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positron emission tomography (PET) imaging for T; and magnetic resonance imaging (MRI) atrophy, CSF total tau (t-tau), and fluorodeoxyglucose (FDG) PET for N [1, 2]. The Framework redefines AD and its progression in terms of the biomarker profile of the condition.

2.0 NIA-AA Framework Application to Clinical Trials

The NIA-AA Framework has the great advantage of focusing on the biology of the AD that comprises the repertoire of targets for pharmacologic treatment of AD with disease modifying therapies (DMTs). There is a synergy between the proposed classification and biologically-based drug development for AD. Likewise, there are parallels between the Framework and the new AD staging system proposed by the U.S. Food and Drug Administration (FDA)[3]. Here the advantages and challenges of using this classification in clinical trials are presented.

2.1 Biomarker-Based Participant Selection

Of the eight categories of the NIA-AA Framework, one applies to primary prevention before any Alzheimer pathobiology is present (A-T-N-) and three apply to Alzheimer's pathologic change or AD (Table 2). The other 4 categories do not meet criteria for Alzheimer's pathology (A-) or have Alzheimer's pathology plus some non-AD cause of neurodegeneration (A+T-N+).

Primary prevention trials may be appropriate for secretase inhibitors such as beta-site amyloid precursor protein cleavage enzyme (BACE) inhibitors where the participants have no AD-type pathologic changes and the goal of the trial is to prevent the initiation of the cascade of events leading to AD in the future[4]. Primary prevention trials could use the Framework to define A-T-N- participants. This might include amyloid PET negative participants with known disease-causing mutations (presenilin 1, presenilin 2, amyloid precursor protein, Down syndrome) or apolipoprotein epsilon 4 (ApoE4) homozygotes at high risk for developing AD[5]. This group of participants is characterized by the absence of any state biomarker of Alzheimer's pathologic change (A-).

Three categories of the Framework apply to AD trials: A+T-N-; A+T+N-; and A+T+N+. These three categories embrace the spectrum of changes from Alzheimer's pathologic change. Tau imaging has shown that the A+T-N- and A+T+N- characterize much of the preclinical period of AD with increasing tau signal shown by PET to appear in in later preclinical and prodromal phases of the illness[6, 7]. Two classes - A+T+N- and A+T+N+ – account for most individuals with symptomatic AD[8–10].

Although the Framework will assist in clinical trials, further biological differentiation will be needed to allow biological targets to be meaningfully related to disease progression. This might be done by rating severity of the ATN changes or by adding additional phase-specific biomarkers[11, 12]. For example, trials could begin with participants whose tau is confined to temporal lobe regions and an outcome would be a drug-placebo difference in spread to wider neocortical regions. Alternatively, atrophy can be quantitated and drug-placebo differences in progression to more severe atrophy captured as an outcome. Such biological

measures have rarely been used to construct trials to date; the Framework provides a plausible means of beginning to plan such trials.

The NIA-AA Framework emphasizes the presence of Alzheimer-related pathologic change (ATN) but does not exclude additional types of pathology that may complicate planning and outcomes in clinical trials. A+T-N+ can be mixed dementia with N being attributable to a concomitant non-AD condition. A+T+N+ can also be mixed dementia with the neurodegeneration coming from AD or an associated condition. Thus, the Framework will be supplemented by other approaches such as excluding patients with cerebrovascular disease by MRI to accurately interpret N. Similarly, many other types of pathology co-occur with AD changes and are not addressed in the ATN Framework. Alpha-synuclein TAR DNA binding protein 43(TDP-43), hippocampal sclerosis, and vascular lesions are frequently present in patients with AD, particularly older individuals. Only ten to 30 percent of patients with AD have pure Alzheimer's pathologic changes[13–16]. Additional biomarkers for these co-occurring pathologies will be needed if they prove to be important from a treatment perspective.

The NIA-AA Framework provides a means of excluding patients with Alzheimer-related pathologies from trials focusing on non-AD dementias such as vascular dementia (VaD), frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD)(Table 2). All these cases would be in the A- category. Some may be T+ by tau PET (e.g., tau-related FTD, PSP, CBD)[17, 18], and most will be N+ unless diagnosed at very early stages of disease. Diagnosis of these disorders will depend on recognizing a compatible phenotype and supportive brain imaging findings. In this setting, the Framework contributes as a means of identifying AD-phenocopies of non-AD disorders [12, 19]. The ATN approach does not prioritize any specific aspect of the biology and allows systems level analyses of the elements in response to trial interventions[20].

2.2 Biomarker-Based Participant Section

A critical aspect of the Framework approach is to insure that the target pathology is present in the trial population. Anti-amyloid immunotherapies and some small molecules require the presence of excessive Aß in the brain and reduction of the Aß burden is evidence of target engagement. The clinical phenotype is not sufficient to insure the accuracy of the AD diagnosis and the presence of the key pathology[12, 21] Amyloid biomarkers are important for diagnostic confirmation even in trials of non-amyloid therapies.

2.3 Clinically-Based Participant Selection

Clinical trials cannot depend exclusively on the biological profile of the participants and must include characterization of the clinical syndrome; clinical benefit or the ability to predict clinical benefit will be required for drug approval. A clinical benefit is the principal outcome of clinical trials of interest to participants and their partners, clinicians, regulators, and payers. The Framework emphasizes biomarkers over clinical features but clinical trials will require consideration of both aspects of AD[12].

Table 3 uses the numeric clinical stage of individuals on the Alzheimer continuum proposed by the Framework and shows the typical clinical assessments that would be used to

characterize the participants in a clinical trial. The clinical stages correspond to the staging system of the Alzheimer's spectrum proposed by the FDA[3]. The ATN classification is juxtaposed with the clinical stage and the assessment instruments. The biological Framework of the Alzheimer's continuum is helpful for characterizing the biomarker state of the participants and will be integrated with clinical staging to construct clinical trials that have populations with sufficiently homogeneous clinical characteristics to allow trial planning including inclusion and exclusion factors, outcome assessments, recruitment, and sample size determination.

The clinical linkages to the ATN Framework are modest. Amyloid status (CSF $Aß_{42}$ or amyloid PET) has a minor impact on cognition over the long preclinical period in which amyloid is present in the brain[22]; correlation between amyloid measures and cognition are weak. Correlations between tau (tau PET and CSF p-tau and clinical measures) are significant in the symptomatic phases of the illness [23, 24].

Recent studies show that tau PET accounts for approximately 30% of the variance on a composite memory test score in the AD Neuroimaging Initiative (ADNI) cohort[25]. Correlations between MRI atrophy and ADAS-cog scores in prodromal AD and AD dementia are in the range of 0.45[24]. These observations suggest that other brain pathologies – inflammation, oxidation, alpha-synuclein, TDP-43, cerebrovascular changes and host-related compensatory factors (e.g., cerebral reserve) contribute importantly to the profile of cognitive changes observed in prodromal AD and AD dementia. These pathologies and the corresponding cognitive deficits may not respond to anti-amyloid or anti-tau therapies. The NIA/AA Framework can establish more homogenous treatment groups; biological heterogeneity and biomarker/clinical disparities are not eliminated.

2.4 Prediction of Progression

Faster disease progression on clinical measures allows detection of a drug-placebo difference in clinical trials with smaller sample sizes. This translates into faster decision-making and could ultimately accelerate getting new therapies to AD patients and those at risk for AD. The NIA-AA Framework provides support for predicting progression [1]. The highest rates of short-term progression are in the A+T+N- and A+T+N+ classes of AD. CSF p-tau levels predict MRI progression in longitudinal studies of patients with mild AD dementia and in cognitively normal participants[26]. FDG PET and t-tau (markers of N in the ATN classification) predict clinical progression to AD dementia in patients with MCI at baseline[27]. Tau PET at baseline predicts progressive cognitive decline but this effect is greater in older than younger individuals[12, 28]. Choosing participants with the progression-prediction ATN biotypes will help insure measurable cognitive decline in the trial period and an improved chance of observing a drug-placebo difference.

2.5 Target Engagement

The NIA-AA Framework is aimed at establishing the biomarker characteristics of the Alzheimer's spectrum and not with other uses of the biomarkers in AD drug development[1]. Development of DMTs depends on demonstrating target engagement in Phase II trials to insure that near and intermediate term steps critical to disease-modification

are being achieved[29]. A successful DMT must exert neuroprotection and this goal will be reflected most closely in a drug-placebo difference on N[30, 31]. A and T are intermediate targets whose modification may result in neuroprotection and disease modification through linked mechanisms.

Amyloid plaque burden on amyloid PET, tau aggregation on tau PET, and CSF measures of $A\beta_{42}$ or p-tau can function as intermediate measures of target engagement. Measurement of tau in trial participants allows tau PET or CSF p-tau to be used as measures of target engagement. Measures could include prevention of tau accumulation in A+T- individuals, spread in A+T+ participants, or reduction of tau in A+T+ participants. The Framework establishes the presence of the target pathology and provides the opportunity for the ATN classification to be used to demonstrate target engagement of A or T.

2.6 Outcomes for Trials of Disease-Modifying Therapies

Successful DMTs will exert neuroprotection[30, 31]. Neurodegeneration in the ATN Framework is assessed by MRI atrophy, CSF t-tau, for FDG PET. FDG PET can be impacted by symptomatic therapies and these effects must be considered when interpreting observations considered indicative of disease modification [32, 33]. Drug-placebo differences in MRI atrophy or t-tau at trial termination would provide the most compelling evidence of disease modification. MRI has often performed irregularly as an outcome in clinical trials, with greater atrophy in the treatment group [34–36], and dependence on this measure as an outcome to support disease-modification has uncertainties. More measures of successful amelioration of neurodegeneration are needed to serve as outcomes in DMT trials.

The Framework provides guidance for uniform reporting of biological outcomes in clinical trials that is critical to building understanding of the relationship of drug mechanisms to their biological consequences[37].

3.0 Discussion

The NIA-AA Framework is a useful advance in biomarker classification of the Alzheimer's spectrum[1]. It uses the ATN biomarkers to establish the continuum, allows staging of trial participants, insures the presence of target pathology, provides a framework of considering ATN as outcomes supportive of disease modification, and facilitates a means of excluding Alzheimer's spectrum individuals from trials intended to address non-Alzheimer disorders.

Two forms of Aß measures are used in the ATN approach – CSF $A\beta_{42}$ and amyloid PET. There is substantial evidence that the most neurotoxic species of Aß is comprised of oligomers with variable lengths of amino acids from dimers to dodecomers and higher order pre-fibrillar species [38–40]. There is no consensus measure of these forms of Aß and the relationship of oligomers to the ATN classification remains to be clarified. Some approaches of anti-amyloid therapy may depend on an effect on oligomers.

The Framework poses a CSF and a brain imaging alternative for each ATN category[1] (Table 1). This is useful and may facilitate trial recruitment by allowing participants with

access to either technology to enter the trial (this is especially important in global trials where access to amyloid PET is limited). The CSF measures of amyloid and amyloid PET are highly correlated [41] but they measure different forms of amyloid and use of the either/or approach may increase the heterogeneity of the trial population with unknown consequences. Similarly the correlation of CSF p-tau to tau PET is significant in AD dementia where tau PET shows extensive changes but not in preclinical AD where CSF p-tau levels are similar to those of AD dementia but PET abnormalities are geographically limited[23, 42, 43]. Tau-PET Standard Uptake Volume Ratios (SUVRs) account for about one-third of the variance of hippocampal atrophy and about 20% of the variance of cortical atrophy among individuals with positive amyloid imaging[44]. MRI atrophy correlates with t-tau in some investigations but the correlations have not been observed in all studies [45–47]. Agreement between MRI volumetric measures and FDG PET (two N measures) is inconsistent across studies[48]. Tau and FDG PET (two N measures) are not well correlated [49, 50]; and agreement between MRI atrophy and t-tau (N markers) is limited[48]. Trial design will need to anticipate the effects of applying the ATN criteria by CSF, imaging, or mixed approaches.

Biomarkers are the best window on the biology of Alzheimer's pathological changes as the brain itself is inaccessible. Investigators employ CSF measures of $A\beta_{42}$ and amyloid PET as surrogates for brain amyloid; CSF p-tau and tau PET as surrogate measures of brain tau pathology; and t-tau, FDG PET and MRI as surrogates for neurodegeneration. Autopsy studies support these relationships but also reveal that correlations between biomarkers and brain changes are imperfect. Neurofibrillary tangles correlate with changes in hippocampal measures observed on MRI in some studies but not others[46, 51, 52]. Plaques do not correlate with MRI atrophy measures[46, 51]. CSF p-tau and t-tau correlate with neurofibrillary tangle burden in some studies by not others [46, 53]. Variability in the correlation of CSF $A\beta_{42}$ to extracellular amyloid plaques observed at autopsy has also been observed [53, 54]. Some of the inconsistencies in the literature may reflect challenges with CSF assay standardization as well as the use of clinical diagnosis of AD unconfirmed by biomarkers in some studies. Progress has been made on both of these fronts.

Trial planners must be aware of the limits of biomarkers as reflections of the state of the pathology in the brain; the latter must be impacted by effective biological therapies.

4.0 Summary

The NIA-AA Research Framework[1] is an important advance in using biomarkers to define the AD spectrum. This approach will be useful in designing clinical trials and has an important role in characterizing the biomarker profile of participants entering trials. The Framework will assist in excluding Alzheimer spectrum participants from trials of non-Alzheimer dementias. The Framework facilitates considerations of target engagement and trial outcomes. The Framework effectively captures the current understanding of biomarkers of the Alzheimer's spectrum using the ATN approach. The eight types of ATN biomarker profiles include one with no abnormalities, four with amyloid changes (one with features of mixed dementia and one limited to amyloid changes characteristic of Alzheimer's pathological changes without AD), and three with non-AD type profiles; most of the

symptomatic forms are comprised of two types (A+T+N-; A+T+N+). Mixed dementias and the complex neuropathology of AD are not addressed in the ATN Framework [13–15]. Characterizing trial participants with multiple biomarkers (specific levels of T and N in A+ individuals, for example) may complicate recruitment while improving the biological definition of the trial population. The imperfect relationships between the two amyloid, two tau, and three neurodegeneration markers may contribute to trial population heterogeneity, and the less-than-complete correlations between biomarkers and brain pathology challenges researchers to refine the Framework. Finally, the limited correlation of cognitive decline with ATN biomarker changes demonstrates that factors outside this repertoire are likely contributing to the cognitive impairment. Biomarkers of these other pathologies and treatments to address them may play an important role in the quest to find DMTs for those with or at risk for AD. The NIA-AA Framework is a key advance in establishing a clinically viable biologically defined characterization of the Alzheimer's spectrum with application to clinical trials.

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Declaration of Interest:

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Table 1.

Biomarkers included the amyloid, tau, neurodegeneration (A,T,N) classification.

Biomarker Class	Cerebrospinal Fluid Marker	Imaging Marker
Amyloid (A)	CSF $A\beta_{42}$	Amyloid imaging
Tau (T)	CSF phospho-tau	Tau imaging
Neurodegeneration (N)	CSF total-tau	MRI; FDG PET

$A\beta_{42}$ – amyloid- beta protein, 42 amino acid length; CSF – cerebrospinal fluid; FDG – fluorodeoxyglucose; MRI – magnetic resonance imaging; PET – positron emission tomography

Table 2.

ATN classification of neurodegenerative disorders including those related to Alzheimer's disease (AD). The three categories most relevant to clinical trials for AD are shaded. The type of trial associated with each group in the classification is noted.

Amyloid (A)	Tau (T)	Neurodegeneration (N)	Comment	Trial Population
Negative	Negative	Negative	Normal	Primary prevention trials; before amyloid is present
Positive	Negative	Negative	Alzheimer pathology; this defines preclinical AD before any changes associated with amyloid have begun	Secondary prevention trials; amyloid is present, tau is not; delay of tau spread as a potential outcome
Positive	Positive	Negative	AD; amyloid and tau changes are present; no effect on neurodegeneration	Secondary prevention trials; amyloid and tau are present, neurodegeneration is not; delay in tau spread or development of neurodegeneration are potential outcomes
Positive	Positive	Positive	AD; amyloid, tau, and neurodegeneration	Treatment trials; all 3 basic biomarkers are present; slowing of progression or delay to milestone are appropriate designs
			This category will also include mixed dementia where AD co-exists with other brain disorders such as cerebrovascular disease. Comorbid conditions contribute to the neurodegeneration component.	Combination treatment trials could include this population; for example, trials including AD and CVD
Positive	Negative	Positive	Alzheimer pathology plus some other cause of neurodegeneration	Combination treatment trials of anti-amyloid agent and drugs addressing concomitant pathology may be warranted
Negative	Negative	Positive	Not AD; neurodegeneration only	Non-AD trials such as VaD, FTD, PSP, CBD
Negative	Positive	Negative	Not AD; elevated tau without neurodegeneration	Non-AD trials of CVD, prion disease, or early tauopathies
Negative	Positive	Positive	Not AD; elevated tau and neurodegeneration	Non-AD trials of VaD or prion disease

CBD – corticobasal degeneration; CVD – cerebrovascular disease; FTD – frontotemporal dementia; PSP – progressive supranuclear palsy; VaD – vascular dementia

Table 3.

Numeric clinical stages of individuals on the Alzheimer continuum, examples of the clinical assessments that would be used to characterize the participants in a clinical trial, and corresponding ATN characteristics at each stage. The Neurological Clinical Staging is consistent with the recent FDA guidance of AD stages (U.S. Food and Drug Administration. Early Alzheimer's disease: developing drugs for treatment; draft guidance for industry. Federal Register; 2018. p. 7060-1).

Numeric Clinical Staging	Clinical Phase	Cognitive/ Composite Assessment	Functional Assessment	Behavioral Assessment	ATN Classification
1	Cognitively normal with no indication of decline	PACC; APCC	No functional deficit	No established behavioral change	A+T-N-
2	Cognitively normal with indication of decline	PACC; APCC	No functional deficit	No established behavioral change	A+T+N- or A+T+N+
3	Prodromal AD	CDR-sb; ADCOMS; iADRS; NTB	ADCS-ADL (MCI version)	MBI/NPI	A+T+N+
4	Mild AD dementia	ADAS-cog; NTB; CDR-sb	ADCS-ADL	NPI	A+T+N+
5	Moderate AD dementia	ADAS-cog; NTB; CDR-sb	ADCS-ADL	NPI	A+T+N+
6	Severe AD dementia	SIB; CDR-sb	ADCS-ADL (severe version)	NPI	A+T+N+

A – amyloid; ADAS-cog – Alzheimer's Disease Assessment Scale – cognitive subscale; ADCOMS - AD Composite Score; ADCS-ADL (MCI) – Alzheimer's Disease Cooperative Study – Activities of Daily Living scale (mild cognitive impairment version); APCC - Alzheimer Prevention Initiative Cognitive Composite; CDR-sb - Clinical Dementia Rating- Sum of Boxes; iADRS - Integrated AD Rating Scale; MBI – Minimal Behavioral Impairment scale; N – neurodegeneration; NPI – Neuropsychiatric Inventory; NTB - Neuropsychological Test Battery; PACC - Preclinical Alzheimer Cognitive Composite; SIB – severe impairment battery; T - tau