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Perspectives

Rethinking the Food and Drug Administration's 2013 guidance on developing drugs for early-stage Alzheimer's disease

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Abstract The February 2013 Food and Drug Administration (FDA) draft guidance for developing drugs for early-stage Alzheimer's disease (AD) creates certain challenges as they guide toward the use of one cognitive outcome to gain accelerated marketing approval for preclinical AD drugs, and a composite clinical scale – the Clinical Dementia Rating Scale in particular – for the primary outcome for prodromal AD clinical trials.

In light of the developing knowledge regarding early stage diagnoses and clinical trials outcomes, we recommend that FDA describe its requirements for validating preclinical AD diagnoses for drug development purposes, maintain the principle for requiring coprimary outcomes, and encourage the advancement of outcomes for early stage AD trials. The principles for drug development for early stage AD should not differ from those for clinical AD, especially as the diagnoses of prodromal and early AD impinge on each other. The FDA should not recommend that a composite scale be used as a sole primary efficacy outcome to support a marketing claim unless it requires that the cognitive and functional components of such a scale are demonstrated to be individually meaningful. The current draft guidelines may inadvertently constrain efforts to better assess the clinical effects of new drugs and inhibit innovation in an area where evidence-based clinical research practices are still evolving.

Keywords: Preclinical Alzheimer's disease; Prodromal Alzheimer's disease; Mild cognitive impairment; Diagnostic criteria; Food and Drug Administration; Regulatory guidance; Disease modification; Drug development; Clinical trials; Clinical outcomes; Composite scales; Neuropsychological tests; Clinical Dementia Rating Scale; Amyloid; Biomarkers

1. Introduction

The Food and Drug Administration's (FDA's) draft guidelines for developing drugs for early-stage Alzheimer disease [1] both advance a number of issues for Alzheimer's disease (AD) therapeutics and create some challenges. The guidelines advance regulatory support for new research diagnostic criteria [2,3] and for biomarkers to enrich trials with participants who have amyloid pathology. They clarify that currently proposed biomarkers are not surrogate markers for clinical outcomes, and those that would be used to support disease modification claims must reflect the progression of the underlying AD pathology. Indeed, they put the prospects for disease modification marketing claims in a realistic context by emphasizing that they are extraordinary, major claims, implying that nearly everybody at risk for AD would need to take the proposed medication [4].

Yet, other guidance on preclinical AD, mild cognitive impairment (MCI) due to AD (prodromal AD), and recommendations for clinical outcomes in drug development are challenging and need to be fixed.

2. Preclinical AD and accelerated approval

The FDA describes preclinical AD as "subtle cognitive deficits [that] may be evident only through the use of

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sensitive measures of neuropsychological performance" [1, p.2]. Sponsors may gain accelerated or provisional approval for a drug for preclinical AD by using one cognitive assessment procedure as the sole, primary efficacy measure in a pivotal clinical trial. The rationale, however, is that the cognitive effect would be reasonably likely to predict clinical benefit. A sponsor would then be required to demonstrate clinically meaningful effects in postmarketing studies.

Identifying people with *preclinical* AD should require evidence for the presence of AD pathology and knowledge that the diagnosis will predict subsequent *clinical* AD. Subtle cognitive worsening or deficits in older individuals are not necessarily related to amyloid or AD pathology, but may be related to age-associated cognitive decline, cerebrovascular changes, trauma, TDP-43 or synuclein proteinopathy, medical illness, medications, or other conditions. Many older individuals who score in lower ranges of neuropsychological test scores may show AD pathology but may not go on to develop MCI or AD [5].

If a preclinical AD diagnostic construct is not validated, then relying on cognitive assessments as a sole, primary efficacy measure for drug approval risks approving drugs for various and ill-defined conditions that do not progress to clinical AD in any reasonable time frame. For example, one can hypothesize cholinesterase inhibitors, cognitive enhancers, neuronal nicotine receptor modulators, memantine, or drugs that may attenuate the synaptic effects of soluble amyloid-β, may have longer term, measurable cognitive effects for preclinical trials participants. The effect, however, may be in those who progress to clinical AD, do not progress to clinical AD, or do not have AD pathology per se. Although salutary cognitive outcomes from safe drugs would be welcomed, the outcomes would not necessarily indicate a treatment specific to AD or predict long-term benefit.

The FDA might better describe its requirements for validating the range of preclinical AD diagnoses, the risk rates for subsequent clinical AD that would be required, and its view on the kinds of drugs that would be appropriate for preclinical AD under its accelerated approval process. Furthermore, the FDA might expand its draft guidelines to include pathways for the development of drugs for age-associated memory impairment, age-associated cognitive decline, and the early manifestations of TDP-43 and synuclein proteinopathies because these are common comorbid conditions and may need to be distinguished from preclinical AD.

Participants in preclinical AD trials are, on average, unlikely to decline substantially during a trial of even several years' duration. Many study volunteers would improve on test scores as a result of the ebb and flow of their preclinical condition, measurement error, misspecification, and misdiagnosis. In this scenario, an otherwise effective test drug will likely not be able to show statistical significance on a sole cognitive assessment unless the drug causes absolute improvement over baseline scores. These circumstances may show efficacy of drugs that have cognitive enhancing, neurotropic, or neuroregenerative effects. Conversely, drugs that attenuate only the progression of AD pathology (and do not reverse it) may fail to demonstrate detectible cognitive effects and, consequently, further development may be halted.

In sum, the accelerated approval scenario appears to favor drugs with cognitive enhancing effects assessed over relatively shorter treatment durations. For postulated disease-modifying drugs without symptomatic effects, much larger samples and longer follow-up periods would be required such that cognitive worsening could be detected in sufficient numbers such that a potential drug effect could be observed.

3. MCI due to AD/prodromal AD and outcomes guidance

The guidelines recognize correctly that MCI due to AD (or prodromal AD) is incipient AD dementia and substantially the same diagnosis. According to the National Institute on Aging–Alzheimer's Association criteria on which the FDA relies, MCI due to AD is defined by concern about cognitive decline, objective evidence of progressive cognitive impairment (nearly always memory), "preservation of independence in functional activities" [2, p. 271] and not meeting criteria for dementia.

The threshold for memory impairment required for the diagnosis of MCI AD [2], for entry into several earlier MCI clinical trials [6], and the Alzheimer's Disease Neuroimaging Initiative [7] is the same as is typically required for an AD dementia diagnosis. Moreover, there is virtual equivalence and substantial overlap in clinical and biomarker values between the more cognitively impaired half of patients with MCI due to AD and the less impaired half of the patients with AD in the Alzheimer's Disease Neuroimaging Initiative [8]. National Alzheimer's Coordinating Center data from the National Institutes of Health-funded AD centers similarly show that more than 92% of individuals diagnosed with mild or very mild AD would fulfill criteria for MCI due to AD as well [9].

The requirement for "preservation of independence in functional activities" is complicated as

> "[p]ersons with MCI commonly have *mild problems performing complex functional tasks* which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their *independence of function in daily life*, with minimal aids or assistance" [2, p. 271] (emphasis added)…. There is generally mild functional impairment for complex tasks, but basic activities of daily living should be preserved, and the person should not meet criteria for dementia [2, p. 273].