

# Primary prevention trials in Alzheimer disease

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**Abstract**—Many new treatments under development for Alzheimer disease (AD) will be disease-modifying rather than symptomatic. Clinical evaluation of these treatments will include require and secondary prevention trials. We describe some of the methodologic challenges in designing primary prevention trials for AD and illustrate these with examples from the ADAPT Study and GEMS Study. Primary prevention trials for AD present many design challenges. In most situations, secondary prevention trials provide the most feasible first step toward primary prevention.

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At present, only symptomatic treatments are available for the therapy of Alzheimer disease (AD), but there is an emerging consensus that disease-modifying treatments represent new opportunities for therapeutic intervention.<sup>1</sup> Disease-modifying treatments are those that may or may not provide any symptomatic improvement, but can slow the biological progression of AD. Such treatments could be started before the development of clinical symptoms, delaying the clinical onset of the disease (i.e., primary prevention). They could also be started after the onset of clinical symptoms with the intent of slowing the progression of the disease already under way (i.e., secondary prevention).

Designing trials to test the efficacy of putative disease-modifying agents is conceptually straightforward but is difficult in practice. In theory, individuals with or at risk for AD can be randomized into control and intervention groups, and the emergence of symptoms, or rate of decline on specified outcome measures, will differ if the intervention is effective. If there is any question that the intervention may be providing a symptomatic effect rather than a disease-modifying effect, the groups can be followed after the discontinuation of the intervention. If only a symptomatic intervention is present, the outcome curves should re-join. But outcomes should stay separated (although declining at different rates) if the rate of disease decline is affected over the time course of the intervention.<sup>2</sup>

Powering both primary and secondary prevention trials depends on knowledge of the future rate of

cognitive decline among persons to be recruited, as well as estimation of the efficacy of the intervention. Here, secondary prevention trials have an advantage. There are already well-established categories of disease definition for probable AD that can be used to define the target population for such trials. Moreover, the rate of decline for AD can be estimated among a likely volunteer population for such trials by examining the placebo-controlled arm from a large number of previous trials and longitudinal studies.

## Design challenges in primary prevention trials.

Some inferences about cognitive decline can be drawn from longitudinal epidemiologic studies, particularly population-based samples. However, without the benefit of many previous trials, the differences among the types of persons who might volunteer for a multiyear intervention trial are difficult to predict. For example, persons motivated to volunteer for such a trial might be more frightened about getting AD in the future, either because of perceived memory difficulties in themselves or because of a positive family history. Either of these would enrich the trial population for persons at higher risk for AD and would lead to a more rapid overall decline in outcome measures in comparison to population-based estimates. Alternatively, persons motivated to volunteer for such trials could be more highly educated, health-oriented volunteers with greater than average motivation and initiative. Such features would skew the trial population to-

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ward lower risk for AD and thus lead to a slower decline in disease outcomes. By any measure, rates of cognitive decline among nondemented individuals are relatively low, meaning that primary prevention trials using cognitive decline as the outcome would require many years to complete, and over this time drop-outs and deaths, unexpected side effects, or the appearance of competing treatments could also influence the success of a trial.

The makeup of a potential trial population and resulting efficiency of the trial can be dramatically influenced by selection criteria for "unaffected" individuals. In an effort to choose trial participants who would decline more rapidly and thus make the trial more efficient, a primary prevention trial could restrict enrollment to persons at increased risk for AD by using the well-established increased risk of age, family history,<sup>3,4</sup> the presence of the APOE  $\epsilon$ 4 allele,<sup>5</sup> or some mild degree of objective cognitive impairment that falls short of actual dementia. Disclosing APOE genotype is controversial at the present time,<sup>6,7</sup> and including trial participants with mild cognitive impairment (MCI) blurs the lines between primary and secondary prevention trials because some of these individuals (depending on the actual criteria employed) may already be in the early stages of AD.<sup>8</sup>

The mechanisms of the treatment intervention being tested may also inform the design of a primary prevention trial and the selection of participants. If the proposed treatment is hypothesized to work only during a biological "window of opportunity" that could close at the onset of clinical symptoms, then enrollment of persons with any degree of cognitive impairment could be counterproductive because many of them would already have early AD. Various types of volunteers might be attracted by different methods of treatment administration (injection, IV infusion, or pill), different side-effect profiles, and the various alternatives available in other competing research studies or available in the marketplace to potential volunteers with or without evidence to support their efficacy. Once patients are enrolled, the actual side-effect profile of a proposed treatment would influence the rate of drop-outs from any given prevention trial.

In addition to the makeup and projected rate of decline among the anticipated volunteers, the design of a primary prevention trial must estimate the efficacy of a proposed treatment in order to design sample size and duration of the trial. A proposed treatment that completely arrests the progression of the disease will require far fewer participants and less time than one that reduces the rate of disease progression by a small percentage each year. This is a substantial obstacle for proposed treatment trials in which the degree of treatment efficacy has never been demonstrated. Even designing Phase II trials for the purpose of gauging efficacy may be difficult (and expensive) when no data are available. A proposed treatment that would be expensive or have

serious side effects might be justified only if the expected efficacy were robust. However, a proposed treatment that was inexpensive and safe might be very worthwhile if taken over many years, even if the efficacy were very modest in the short term. Ironically, a modestly efficacious treatment even if safe and inexpensive, might be the most difficult around which to design a trial because it would might require an exceedingly long trial to demonstrate efficacy. Most current prevention trials have used relatively safe, well-known medications with familiar therapeutic profiles (table 1).

Among other considerations in designing primary prevention trials are the choice and stability of outcome measures for the trials. Thus far in the development of all AD clinical trials, outcome measures have relied directly on cognitive testing or have indirectly combined cognitive testing with neuromedical evaluation to assess "conversion" from one clinical state to another (such as from normal to dementia or from MCI to dementia). Because cognitive performance varies considerably, a large number of participants must be tested to demonstrate changes among groups. Should well-validated and stable proxy measures of disease progression become available, such as structural, functional, or disease-dependent imaging studies, these could be substituted for cognitive outcomes that are currently used, with a significant potential gain in study efficiency.

Other methods for conducting primary prevention trials are "add-on" studies taking advantage of clinical trials that are being conducted for other purposes (table 1). These are difficult to execute successfully because neither the recruitment nor the outcome measures are designed with AD in mind.<sup>9</sup>

**Two illustrative examples: the ADAPT Study and the GEMS Trial.** Several primary prevention trials have been attempted or are now under way (see table). We present brief illustrative summaries of two such trials, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT Study) and the Ginkgo in Evaluation of Memory (GEM) Study.

The ADAPT Study is an NIA-funded trial stimulated by epidemiologic studies and some small trials that suggested a protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) in AD.<sup>10</sup> ADAPT was designed as a three-arm parallel, multicenter, randomized placebo-controlled trial of naproxen and of the selective COX-2-inhibiting NSAID celecoxib, with enrollment beginning in the year 2000. Planned outcomes were incidence of dementia and AD and the trajectory of age-related cognitive decline.<sup>11</sup> To enrich the study population for persons at greater risk for AD, enrollment was restricted to persons 70 years of age or older who had at least one first-degree relative with AD-like dementia. In keeping with some epidemiologic studies implicating a protective effect of NSAIDs and suggesting that efficacy might be greater if exposure occurred several years before the onset of clinical symptoms,<sup>12</sup> enrollment

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**Table Primary prevention trials in Alzheimer disease**

| Study                                | Agent                                | Enrollment criteria symptomatic for cognitive difficulties          | Number enrolled or to be enrolled | Planned duration | Currently active  | Outcome measures                               | Results  |
|--------------------------------------|--------------------------------------|---|-----------------------------------|------------------|-------------------|--|--|
| ADAPT <sup>11</sup>                  | Naproxyn, celecoxib                  | Cognitively screened, $\geq$ age 70, first-degree relatives with AD | 2,496 enrolled                    | 7–10 years       | Treatment stopped | Conversion to dementia and cognitive decline   | Not yet available  |
| GEM <sup>14</sup>                    | <i>Ginkgo biloba</i> extract         | Asymptomatic $\geq$ age 75  | 5,000                             | 5 years          | Active            | Incident dementia or cognitive tests           | Not yet available  |
| HERS <sup>15</sup>                   | Estrogen and medroxyprogesterone     | Asymptomatic women, mean age 67                                     | 1,063                             | 4.2 years        | Completed         | Cognitive tests (add-on)                       | One test improved  |
| Heart Protection Study <sup>16</sup> | Vitamins E, C, and beta-carotene     | Asymptomatic with cardiovascular risk factors, age 40–80 years      | 20,536                            | 5 years          | Completed         | TICS and incident dementia (add-on)            | No difference between treated and untreated arms                                 |
| PREADVISE                            | Selenium, vitamin E                  | Asymptomatic men, $\geq$ age 60                                     | 10,400                            | 12 years         | Completed         | Incident dementia and cognitive tests (add-on) | Not yet available  |
| WHI-PERT <sup>17,18</sup>            | Estrogen and medroxyprogesterone     | Women without dementia, ages 65–80                                  | 4,532                             | 4 years          | Completed         | Incident dementia, MCI and 3MS scores          | Treated subjects had elevated risk of dementia and worse 3MS scores              |
| WHI-ERT <sup>18,20</sup>             | Estrogen                             | Women without dementia, ages 65–80                                  | 2,497                             | 5 years          | Completed         | Incident dementia, MCI and 3MS scores          | Treatment group had elevated risk of composite MCI/dementia and worse 3MS scores |
| Heart Protection Study <sup>21</sup> | Simvastatin                          | Asymptomatic with cardiovascular risk factors, age 40–80 years      | 20,536                            | 5 years          | Completed         | TICS <sub>m</sub> at last visit (add-on)       | No difference between treatment groups   |
| GUIDAGE                              | <i>Ginkgo biloba</i>                 | Subjective memory complaints, $>$ age 70                            | 2,600                             | 4 years          | Ongoing           | Incident dementia                              | Not yet available  |
| PHS-II                               | Vitamin E, folic acid, beta-carotene | Asymptomatic, $>$ age 65  | 10,000                            | 9 years          | Ongoing           | Telephone cognitive testing                    | Not yet available  |

Modified from Sano,<sup>9</sup> with permission.

was restricted to persons who had no demonstrable cognitive impairment on neuropsychological testing. The ADAPT Study mailed several million invitations to Medicare recipients surrounding the six study sites and screened responders to enroll 2,496 participants. Over their average 21 months after randomization (~4,600 person-years), 11% of those enrolled were no longer in contact with the trial for a variety of reasons. Study outcomes were far fewer than expected for this enriched population, and the investigators therefore proposed to enroll more participants and to increase the study duration, or both. However, treatments within the ADAPT Study were halted after the Adenoma Prevention with Celecoxib trial revealed widely publicized results showing in-

creased risks for cardio- and cerebrovascular morbidity with celecoxib, and the safety data in ADAPT suggested the possibility of a similar increase in such risk with naproxen.<sup>13</sup> ADAPT has been following participants without treatment to further study these safety issues and also to learn whether there is an effect on dementia incidence that results from the exposure of subjects to NSAIDs in the treated groups compared to placebo.

The ADAPT Study demonstrated that recruiting older persons for a long-duration clinical trial can be arduous and that, even when a trial uses common medications with apparently well-understood risks, new information about side effects can have a disruptive effect. Despite attempts to enrich the trial

using older persons with family histories of AD, the strategy of pre-screening to exclude subjects with cognitive impairments, coupled with the “healthy volunteer” effect, yielded a trial population with very low incidence rates, at least in its first few years of observation.

The GEM Study is an ongoing double-blind, placebo-controlled, randomized trial to assess the ability of *Ginkgo biloba* extract to prevent dementia and AD, with the primary outcome being dementia/AD incidence.<sup>14</sup> There are several secondary outcomes, including effects on rates of age-related cognitive change, cardiovascular, peripheral vascular, and cerebrovascular disease, mortality, and functional abilities. For GEM Study recruitment, no family history was required of potential subjects, the minimum age of entry was 75 years, and subjects were allowed in the study if they had some degree of mild cognitive impairment in one cognitive domain. This trial completed recruitment of more than 3,000 elderly volunteers over 21 months at four sites, but a healthy cohort effect was also seen in this study, with lower than expected initial incidence rates of dementia. Over the several years of the study the incidence rate has increased steadily and now approximates that in many population studies. GEM is expected to be completed in 3 years.

**Summary and Conclusions.** This is an exciting time of discovery in our basic understanding of AD, and a broad variety of treatments with disease-modifying effects are under development. The ADAPT Study and the GEM Study are two of a small number of studies that offer insights into the practice and pitfalls of conducting primary prevention trials, and data gleaned from these and other seminal primary prevention trials will aid in the design of future trials. Primary prevention trials for AD may seem more desirable since they intervene at an earlier pathological stage of the disease, and if effective could prevent or delay disease symptoms altogether. However, most disease-modifying treatments will probably be explored first in secondary prevention trials, which, while decreasing the chance of a beneficial effect by intervening at an earlier stage, can be accomplished with fewer participants and in a shorter time frame.

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