Editorial

Fixing Alzheimer Disease Trials by Improving Process and Methods

The current state of Alzheimer's disease drug development is that only cholinesterase inhibitors and memantine are approved treatments, the development of new therapeutics seem stalled, and promising drugs appear not to translate efficacy from animal to man and from early to later phases. Both the drugs and clinical trials methods are blamed [1,2].

Methods are blamed especially when it seems that the placebo groups are not behaving as expected, as current trials designs depend on the placebo group to worsen over the length of a trial in order to detect a stabilizing effect for the active drug [1,2]. Many, often contradictory, explanations and speculations for failed trials or null results are offered: the placebo patients show "less than expected" worsening; the outcomes are inadequate and insensitive; co-existing medical conditions or use or non-use of cholinesterase inhibitors attenuate outcomes; and the conflicting arguments that more or less severe patients respond better.

Moreover, phase 2 and 3 clinical trials are inherently complicated, resource intensive endeavors with high probabilities for failure. Together, phase 2 and 3 consume 48% of the costs for each drug launched, may cost on average $185 million and $235 million, respectively [3], and are more expensive for Alzheimer's disease. Phase 2 studies thus far have not predicted phase 3 success, mainly because the trials are generally too small and underpowered to assess efficacy, thus markedly increasing costs for phase 3 [3].

In this issue of *Current Alzheimer Research*, Kenneth A Kobak, Robert E. Becker, and Nigel H. Greig speak to the importance of Alzheimer's disease clinical trials methods from two complementary perspectives. Kobak emphasizes the importance of doing outcomes ratings correctly [4]. The gist of his assessment is that mediocre inter-rater reliability, lack of standardization, and scoring procedures contribute to inflation of baseline scores, expectation biases in follow-up scores, and lack of accuracy. Becker and Grieg analyze three failed clinical trials programs to identify methodological lapses [5]. They argue that errors are unavoidable in complex systems such as multicenter trials, but that 'preemptive error management' using checklists would improve the quality of trials and minimize errors.

Kobak's fix is selecting and training site raters to ensure accurate measuring and using highly educated and trained centralized raters, blind to the protocols, to do outcomes assessments via video. Becker's and Grieg's fixes include using checklists to help anticipate and correct errors. A common theme between the authors is measurement variance: where it comes from, why there's too much of it, and the need to constrain it.

The articles appear in *Current Alzheimer Research* at a time of increasing phase 3 trials failures and proposals for new Alzheimer's disease diagnostic criteria that use biomarkers to determine diagnosis. For example, the γ-secretase inhibitor semagacestat, failed in two trials of more than 2600 patients demonstrating unexpected toxicity and lack of efficacy [6]. Dimebon, a drug with unclear actions relevant to Alzheimer's disease, failed to demonstrate any efficacy in a phase 3 trial after a phase 2 trial presented results that seemed too good to be true to some people.

Refined, draft diagnostic criteria for Alzheimer's disease, mild cognitive impairment due to Alzheimer's disease, and "preclinical" Alzheimer's disease, sponsored by the Alzheimer Association and introduced in July 2010 (http://www.alz.org/research/diagnostic_criteria) gained considerable attention from the popular press [7]. More recently, a different *ad hoc* expert group proposed a full lexicon for Alzheimer's disease diagnoses across a spectrum from preclinical, at-risk, to dementia [8].

WRONG THERAPEUTIC TARGETS?

To be sure, the most likely reasons for failures in phase 3 are ineffective drugs. Alzheimer's disease therapeutics is a particularly formidable challenge as there are no validated targets but rather lots of potential targets. The most advanced science, however, has developed around the amyloid cascade as early, perhaps seminal, pathological events, potentially triggering neurodegeneration. Consequently, much drug development research has targeted the production and elimination amyloid-β.

Thus far anti-amyloid trials have not been successful even though some showed predicted effects on their targets. For example, an Aβ vaccine [9] and a monoclonal Aβ antibody [10] both reduced plaques and fibrillar amyloid but didn't appear to have any therapeutic effect in the very small sample size studies. These classes of drugs, antibodies, and vaccines continue in development and may yet prove effective. Their future success may depend on the severity of patients enrolled into trials, the outcomes, and the quality of the trials methods.

Current failures, however, discovered late in the drug development process are demoralizing, enervating, and may cause broad swaths of the community to lose interest. We should not have to enroll thousands of patients in phase 3 in order to discover that a drug is ineffective, the dose range is wrong, is too toxic, or trials methods are suspect. In traditional drug development large phase 2b and 3 trials are considered confirmatory trials of efficacy and safety that were previously established in earlier, "proof of concept" and dose-finding phases. "Proof of concept" studies sometimes are designed to demonstrate target engagement when there are validated drug targets for the illnesses. Becker and Greig suggest methods that might enhance the probability of success in this respect.

How we do early phase development, decide whether or not to advance drugs to later phases, and do the later phase trials needs to be reconceptualized. However, if one is going to base a phase 3 program on an optimistic interpretation of phase 2 results then at least the phase 2 trial should be conducted under the best conditions from which to generate inferences. As Kobak, Becker and Grieg demonstrate, this is

often not the case as the trials sponsors and investigators often tend to give short shrift to methods.

NEW DIAGNOSTIC CRITERIA WITH AN EYE TOWARDS CLINICAL TRIALS

A significant impetus for new diagnostic criteria was frustration with clinical trials outcomes and the desire to use advances in biomarkers to identify broader groups of Alzheimer's disease patients with the hope that drugs could be tested early, before more extensive neurodegeneration, and tested more specifically in patients who demonstrate Alzheimer-related pathology. There is also hope that diagnostic biomarkers could be used as indirect or surrogate outcomes for clinical trials. Thus, new criteria are also attempts to improve trials methods by refining sample selection.

The *ad hoc* workgroup that proposed a lexicon for unifying Alzheimer's disease definitions used biomarkers as the controlling diagnostic criterion [8]. They require a positive biomarker in order to place a person on an Alzheimer's disease continuum; otherwise an Alzheimer's diagnosis cannot be made. Next they require episodic memory impairment as the clinical phenotype that is further characterized as dementia or prodromal Alzheimer's disease depending on severity.

Other expert groups sponsored by the Alzheimer's Association offered nomenclature and criteria for three diagnoses – Alzheimer disease dementia, mild cognitive impairment due to Alzheimer disease, and preclinical Alzheimer disease – and also make biomarkers the key diagnostic construct.

Thus a combination of a specific biomarker and clinical expression could be used to select patients who are transitioning through a certain, hypothesized 'sweet spot' for the drug being tested. The belief here is that inclusion criteria diagnoses with biomarkers can help fix trials, creating more homogeneous samples that would show less between- and within-subject variance on the study outcomes scales. If patients are at an earlier stage then perhaps fewer would be needed. This however, may be illusory, and current evidence does not support that a biomarker identifies patients who are less heterogeneous on their outcomes [11]. Moreover, selecting patients based on biomarkers or early clinical presentations would require greater skill from the research sites and make recruitment more difficult.

CONCLUSIONS

In sum, many factors affect trials in Alzheimer's disease, not the least of which are the inherent heterogeneity of patients, imprecision of the ratings, sites, and clinical course. This is coupled with the facts that even in long term trials there is little mean change on rating scales, and most trials are undersized and underpowered, or at best powered for unrealistic expectations about the drugs' effects. This means that experimental drugs that might in actuality have modest yet clinically meaningful effects may not be recognized with current trials methods, while ineffective drugs may be misidentified as effective when they are not.

Current reactions to trials methods difficulties are to test drugs earlier in the clinical course, for a longer follow-up, and to use "more sensitive" outcomes [11] Kobek and Becker and Grieg demonstrate that methods and the way trials are done – the process factors – may be more important than the structural designs of trials and that trials can be done better.

DISCLOSURES

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