What are the Optimal Cognitive Outcomes for Trials in Preclinical Alzheimer’s Disease?

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METHOD

The Methodological Question Being Addressed
What are the essential properties of cognitive tests which make them effective diagnostic and outcome measures for trials in preclinical Alzheimer’s Disease?

METHODS

The Preclinical AD Workgroup Recommendation:

- Similarity, additional work is required to identify and validate neuropsychological and neurobehavioral measures to detect the earliest clinical manifestations of AD.
- Ignore the progress already made by numerous groups who have long been using such procedures to detect change in cognitive function in unpaired individual, both deterioration and improvement.
- In this poster, examples of tests which are and which are not suitable for such applications will be presented.

RESULTS

Neuropsychological Tests

- The majority of the procedures currently used to measure cognitive function in clinical trials are based on tests the validity of which have not been adapted/adapted from the field of neuropsychology or created by non-psychologists. An important feature of such tests is that most were not designed for repeated use; consequently, most have few if any parallel forms as a threat of training effects was not considered in test design.

Training Effects

- Practice effects
  - determines the need for practice sessions before the start of the trial
  - Equivalent forms
    - for repeated testing over the course of the trial

- Longitudinal data
  - information should be available on expected change over the course of the trial, which is helpful for making power calculations

- Consistency over time
  - some tests were at ceiling levels at baseline and showed no detectable training effects which persisted up to 6 years
  - This may influence the reliability of results obtained from the following calculations:

- Uniform Criteria/Requirements for Optimal Cognitive Assessment Instruments

- Sensitivity range
  - absence of ceiling and floor effects

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can such tests detect decline in healthy elderly volunteers with the same cognitive performance as those in Preclinical AD?

- Are automated tests new to clinical trials including those into pathologic aging and dementia?
- Have they proven sensitive?
- Examples will be given from one such procedure

Automated tests designed for repeated testing

- Are such tests sensitive to treatment effects in patients with MCI or dementia?
- Yes - data from The CDR System

DISCUSSION

- Over the last 25 years considerable evidence has accumulated that many widely used scales and neuropsychological tests are not fit for the purpose of repeated testing in normal individuals

- This however has not deterred the field from still employing such procedures (e.g. in the TOMORROW study)

- In contrast automated cognitive tests have been available since 1988, and computerised systems exist which have already proven sensitive outcome measures in trials similar to those being conducted in preclinical AD

- Automated methodologies designed for repeated use in clinical trials must be considered if the field is to move forward in developing treatments for pathological cognitive aging

The Work Group concluded that computerised testing is likely to be more sensitive than the standard tests which are used in ADNI & thousands of other studies

- Automated computerised testing can have clear advantages for clinical trials in this field

- Automated procedures have been shown to be more sensitive than the standard tests which are used in this field, and the sensitivity to anticholinesterases in AD also has been established

- Given the previously noted importance of assessing attention and information processing speed in this field, computerised tests can provide optimal procedures for assessing changes in these functions. Some tests of attention and information processing speed are on computer.

- Crucial requirements for computerised testing include the recording of responses via simple response buttons or touch screens, not the keyboard.

- The Work Group concluded that computerised procedures should be used together with these validated procedures in the field (e.g. the ADAS-cog) so that the comparable utility and sensitivity of the two types of testing can be identified. It clear advantages of computerised procedures are demonstrated, such procedures might supersede existing methods.

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