THE ROLE OF COGNITIVE TESTS IN TRIALS OF DRUGS TO TREAT AGE-RELATED COGNITIVE DECLINES: BIOMARKERS OR ENDPOINTS?

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Cognitive function can only be directly measured by requiring someone to perform a task involving aspects of mental performance and assessing how well the task is performed. Tens of thousands of tests of cognitive function have been developed and used in research for over 150 years. While all such tests can assess to some degree the quality of function, the vast majority of such tests are not suitable for assessing changes in function over time. To reliably assess change, tests require alternate forms for repeated administration, and also to assess all aspects of performance. Computerised tests can be particularly useful by enabling the speed of responses to be directly linked to the accuracy of each response. Computerised tests of cognitive function have now become widely available. There are a number of proprietary systems in widespread use, all well validated and with established utility and reliability. The presentation will consider data from one such system, the CDR System, which has been used in over 1100 clinical trials worldwide since the mid 1980s. Data will be presented from a database of over 5000 healthy adults aged 18 to 87 years showing that major aspects of cognitive function including attention, working and episodic memory decline decade by decade from the twenties on. The methods of Salthouse have been applied to these data to show that as with his large databases, these declines are marked, start at an early age, occur in all major domains and in most people. These declines have been termed Age-Associated Memory Impairment (AAMI) or Age-Related Cognitive Decline (ARCD). As these declines occur in healthy individuals who are functioning normally for their age, there is no appropriate biomarker, and thus for compounds designed to counteract these age-related changes, cognitive tests must be the study endpoints. A range of compounds which can reduce age-related declines will be mentioned, including standardised extracts from natural substances including ginkgo and ginseng. This year joint workgroups from the National Institute for Ageing and the Alzheimer's Society have published research guidelines for the preclinical stages of Alzheimer's disease (AD) (Sperling et al, Alzheimer's & Dementia 2011 7:280-292). The preclinical stage of AD will include individuals will are functioning normally, and may have a biomarker which suggests a likelihood of eventually developing AD. In such trials, widespread repeated application of sensitive cognitive tests will help identify individuals who show abnormal rates of cognitive decline, and who may be in the preclinical stages of AD. Mild-Cognitive Impairment (MCI) is currently considered the earliest stage of AD detectable with cognitive tests, though some research suggests that the declines may start earlier, and this may be confirmed when large trials of preclinical AD are conducted. A recent paper has shown that the cognitive impairment in MCI is a more robust predictor of conversion to AD than most traditional biomarkers (Gomar JJ et al, Arch. Gen. Psychiatry 2011, 68: 961-969). Thus in MCI, as everyday function is supposed not to be compromised, cognitive function tests would serve as an adequate endpoint. In AD and other dementias, the various traditional CSF and imaging biomarkers are already well advanced, and often do not change markedly as the disease progresses. In such cases, the quality of everyday behavioural function would be an appropriate endpoint, as would cognitive function testing. Ultimately, as dementia can occur without traditional biomarkers, and individuals with advanced biomarker pathology may function normally, tests of cognitive function together with measures of everyday function will be the ideal endpoints for novel treatments.