A Review of 186 Clinical Trials Reporting Cognition Enhancement Using a Single Computerized System Designed Specifically for Clinical Neuroscience

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THE CDR SYSTEM

- As human longevity steadily grows in more fortunate world regions, cognition enhancement has become a "hot topic" and is currently arousing intense public and scientific debate.
- While definitions vary, cognition enhancement can be defined as improved ability to perform tasks involving mental ability, either by countering impairment, or by producing improvement above existing levels.
- The principal, and arguably only direct, objective measure of cognitive ability involves the use of tasks that demand mental efficiency, i.e. cognitive tests
- This paper concerns a computerised test system designed by the author which had its roots in a PhD program which started at Reading University (UK) in 1972.
- The research used nicotine and scopolamine as tests to determine whether the brain functions differently, systems were involved in the control of human attention
- It rapidly became evident that to detect subtle cognitive improvements in healthy young subjects with nicotine, automated procedures that captured speed of cognitive processes as well as the accuracy of performance were essential.
- Static laboratory based computers of the 1970s offered the first solutions, while the portable laboratory microcomputers of the early 1980s allowed cognitive testing to migrate from the laboratory to diverse clinical settings and even patients homes

THE CDR SYSTEM

- 186 clinical trials conducted from 1975 to the present described in:
  - 146 peer-reviewed publications
  - 38 published conference abstracts
  - 3 unreported conference abstracts
  - 7 peer-reviewed publications of studies with negative results

Data from:

- 5,765 Healthy volunteers
- 1,847 - Aged 5 to 17 years
- 2,696 - Aged 18 to 40 years
- 986 - Aged 40 to 65 years
- 1,647 - Aged 65 and above
- 8,165 patients from 33 different clinical conditions

CLINICAL POPULATIONS

- 18 Age Associated Memory Impairment (AAMI)
- Alzheimer's disease (AD)
- ADHD both Childhood & Adult
- Coronary Artery Bypass Patients (CABG)
- Carotid Endarterectomy Patients
- Chronic Fatigue Syndrome (CFS)
- Cocaine Dependents
- Dental Anxiety Patients
- Dementia with Lewy bodies (DLB)
- Epilepsy
- Fibromyalgia
- Hepatic Encephalopathy
- Hypertension
- Kidney dialysis Patients
- Mild-Cognitive Impairment (MCI)
- Major Depressive Disorder (MDD)
- Nicotinopathy
- Neurological Oncology
- Breast cancer
- Haematological disorders
- Tumour
- Parkinson's disease
- Parkinson's disease dementia (PDD)
- Post-Operative Cognitive Decline (POCD)
- Post-Menopausal Female
- Recreational Drug Users
- Reduced Cardiac Vascular Reserve
- Shift-Work Sleep Disorder
- Sleep Apnoea
- Stimulant Abusers
- Stroke
- Unemployed

INTERVENTIONS WHICH IMPROVE COGNITIVE FUNCTION

- 18 Age Associated Memory Impairment (AAMI)
- Alzheimer's disease (AD)
- ADHD both Childhood & Adult
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NEGATIVE STUDIES

- 18 Age Associated Memory Impairment (AAMI)
- Alzheimer's disease (AD)
- ADHD both Childhood & Adult
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- Carotid Endarterectomy Patients
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QUESTIONS TO BE ADDRESSED

- Can a single system detect improvement to cognitive function in a wide range of studies?
- Can patients including those with dementia perform the same tests as those used in volunteers?
- Do separate cognitive test systems need to be developed for each individual clinical condition to detect enhancements, or can one system work for all?

Table: Table guide

<table>
<thead>
<tr>
<th>STUDY CATEGORY</th>
<th>COGNITIVE FUNCTION IMPROVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Results</td>
<td>▲ = statistically significant enhancement</td>
</tr>
<tr>
<td></td>
<td>▼ = no significant change</td>
</tr>
<tr>
<td></td>
<td>▼ = significant impairment</td>
</tr>
<tr>
<td></td>
<td>0 = domain not assessed</td>
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</tbody>
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DISCUSSION

- The CDR System was developed to detect enhancements in cognitive function.
- Each task was introduced only once its ability to detect enhancement had been reliably established.
- Importantly, to detect enhancement, cognitive testing needs to be repeated over hours, days, weeks or even years in clinical trials.
- An early feature in the development of the System was the recognition that training effects and practice effects could obscure therapeutic improvements to cognition.
- Repeated pre-study training of volunteers and all patient populations on all CDR System tests has always been an essential requirement for the CDR System.
- Training effects also regularly occur in clinical trials due to the absence or insufficient number of validated and equivalent alternate forms of the tests employed.
- Volunteers and even patients with dementia show gains with repeated testing due to familiarity with the task materials.
- Most tests commonly used in drug development have no or only limited alternate forms, i.e. most neuropsychological tests as well as the ADAS-cog, NTBI & MATRICS Battery, 'this absence being the cause of numerous failures by such tests to detect improvements in recent years.'
- This major problem was recognised early in the development of the CDR System & every test has numerous validated and alternate forms, such that no set of test stimuli is ever repeatedly presented to a study participant in any clinical trial.

CONCLUSIONS

- To our knowledge, this is the largest database ever assembled of cognitive enhancement identified with a single test or test system.
- The answer to the question of whether a single system can be used in a diverse range of conditions to detect cognition enhancement approaches a positive yes.
- Further versions of these Tables will include the identification of the relative effect sizes of the various improvements detected.
- Interest is now turning to preclinical Alzheimer's disease due to the notable, numerous and repeated high profile failures of recent years in the development of novel therapies to treat Alzheimer's disease.
- Large long-term trials are already being conducted and many are planned in healthy middle aged and elderly populations, identified to be at risk of developing Alzheimer's disease.
- In February 2013 the FDA issued draft guidelines for such trials which states: "we consider the use of a composite scale, validated in early stage patients to assess cognition and function as a single primary efficacy outcome measure, to be appropriate".
- Automated assessments of cognitive function such as that described in the current document will be a practical solution for such clinical trials.
- Over 60 studies described in the Tables and contained in the following citations attest to the suitability of the CDR System for such trials.