Automated assessment of cognitive function in age-related disorders and the dementias

Professor Keith A. Wesnes
PhD Thesis
Sponsored by Medical Research Council
1973-1976

THE EFFECTS OF NICOTINE AND SCOPOLAMINE ON HUMAN ATTENTION

KEITH WESNES
CORE CDR TESTS

ATTENTION, CONCENTRATION, VIGILANCE
- Simple Reaction Time
- Choice Reaction Time
- Digit Vigilance

WORKING (SHORT-TERM) MEMORY
- Articulatory Loop
- Spatial Working Memory

EPISODIC (LONG-TERM) MEMORY
- Word Recognition
- Picture Recognition
Quality of Episodic Memory

![Graph showing the quality of episodic memory across different age bands. The x-axis represents age bands (18-25 Y, 40 Y, 50 Y, 60 Y, 70 Y, 80 Y) and the y-axis represents msec. The graph indicates a decrease in msec as age increases, with the highest values observed in the 18-25 Y age band.](image-url)
POWER OF ATTENTION

Age Band
18-25
26-30
31-35
36-40
41-45
46-50
51-55
56-60
61-65
66-70
71-75
76+

1050
1100
1150
1200
1250
1300

Age Band
18-25
26-30
31-35
36-40
41-45
46-50
51-55
56-60
61-65
66-70
71-75
76+
POWER OF ATTENTION

n=2036

RT (msec)

age-bands years
Sensitivity to effects of ageing: 6-77 years

Overall Reaction Times

<table>
<thead>
<tr>
<th>Age-bands years</th>
<th>6-10</th>
<th>11-15</th>
<th>16-20</th>
<th>21-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>60 plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT (msec)</td>
<td>2000</td>
<td>2200</td>
<td>2400</td>
<td>2600</td>
<td>2800</td>
<td>3000</td>
<td>3200</td>
<td>3400</td>
</tr>
</tbody>
</table>
Bibliography for ginkgo/ginseng and memory


DOI 10.1007/s002130000533.

ORIGINAL INVESTIGATION

K.A. Wesnes · T. Ward · A. McGinty · O. Petrini

The memory enhancing effects of a Ginkgo biloba/Panax ginseng combination in healthy middle-aged volunteers
Effect of ispronicline, a neuronal nicotinic acetylcholine receptor partial agonist, in subjects with age associated memory impairment (AAMI)

Geoffrey C. Dunbar  Clinical Development and Regulatory Affairs, Targacept Inc., Winston Salem, USA.

Figure 1  Results for the CDR factor power of attention change score, for Ispronicline 50 mg, on day 1 (2 and 4 hours) and day 21 (0, 2 and 4 hours)  
\[ a = \text{ANOVA } p\text{-value for both periods and all time points} \]
Detrimental effects of hypertension on cognitive function in the elderly (70 to 89 years)

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive</th>
<th>Normotensive</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=106</td>
<td>n=116</td>
<td></td>
</tr>
<tr>
<td>Speed of Cognition</td>
<td>6388</td>
<td>5952</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Executive Function</td>
<td>148</td>
<td>263</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>220</td>
<td>241</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Continuity of Attention</td>
<td>92</td>
<td>92</td>
<td>n.s.</td>
</tr>
<tr>
<td>Working Memory</td>
<td>160</td>
<td>175</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Study on COgnition & Prognosis in the Elderly (SCOPE)

- multinational international trial
- 4937 hypertensive subjects aged 70-89 years
- angiotensin II type I (AT1) receptor blocker, candesartan cilexetil
- randomised, double-blind, placebo controlled, design
Correlations between MRI identified hyperintense lesions and cognitive function

- 154 elderly volunteers (70+), MMSE > 24
- MRI 1.5-T GE Scanner
- Power of attention, speed of memory and executive function were significantly associated with lesions in caudate, thalamus and internal/external capsule but not putamen and globus pallidus.
- Episodic and working memory, and sustained attention not associated with lesions in any of these areas.

Profile of Neuropsychological Deficits in Older Stroke Survivors without Dementia

Clive Ballard  Sally Stephens  RoseAnne Kenny  Raj Kalaria  Martin Tovee  John O’Brien

Institute for Ageing and Health, Wolfson Research Centre, Newcastle upon Tyne, UK
Early Cognitive Deficits

The proportion of stroke patients meeting the criteria for early cognitive impairment varied greatly depending upon the criteria used, with 17% meeting criteria for amnestic MCI and 26% meeting the criteria for AACD based upon memory deficits but more than 70% meeting criteria for AACD based upon CRT performance. Thirty-two percent met the more global criteria for CIND. A detailed breakdown is shown in table 1.
Association Between Mild Vascular Cognitive Impairment and Impaired Activities of Daily Living in Older Stroke Survivors Without Dementia

Sally Stephens, BSc,* Rose Anne Kenny, FRCP,* Elise Rowan, PhD,* Raj N. Kalaria, FRC Path,* Michael Bradbury, MSc,* Ruth Pearce, BSc,* Keith Wesnes, PhD,† and Clive G. Ballard, MRC Psych, MD‡

PARTICIPANTS: Three hundred thirty-nine stroke survivors without dementia, aged 75 and older.

MEASUREMENTS: Neuropsychological assessments were completed 3 months poststroke. Activities of daily living (ADLs) were evaluated using the Bristol scale. Operationalized criteria, including cognitive impairment no dementia (CIND), were applied for mVCI.

RESULTS: Significant impairments of ADLs were evident in mVCI (CIND vs no CIND; basic care: \( z = 3.2; P = .001 \), intermediate care: \( z = 3.6; P < .001 \), complex management: \( z = 4.5; P < .001 \)) but varied according to the profile of cognitive impairments. Patients with attentional or global impairments had more severe functional disability than patients with isolated memory deficits, with an intermediate level of dysfunction in patients with executive impairments.

• The CDR choice reaction time task correlated significantly with more than half of the items on the scale (food preparation, eating, drink preparation, dressing, bathing, using the toilet, transferring, orientation to time, using the telephone, shopping, games and hobbies, driving or using transport).

• Non-automated assessments of executive function correlated only with eating and shopping, and memory only with dental care.

• Linear regression analysis showed the attention score to be the only measure associated with disabilities in self-care tasks.

Utility, Reliability, Validity & Sensitivity in the Dementias
THE COGNITIVE DRUG RESEARCH COMPUTERIZED ASSESSMENT SYSTEM FOR DEMENTED PATIENTS: A VALIDATION STUDY

P. M. SIMPSON*, D. J. SURMON†, K. A. WESNES* AND G. K. WILCOCK‡
*Research Director, Cognitive Drug Research, 13 The Grove, Reading, RG1 4RB, UK; †Research Psychologist, ‡Professor in Care of the Elderly, University of Bristol, Department of Care of the Elderly, Frenchay Hospital, Bristol, BS16 1LE, UK
## Independent ability of CDR tests to discriminate clinical groups

Table 2. Means and ranges of the scores on the assessment procedures for the three patient groups, together with the significance of the comparisons of the control group to the demented and probable AD groups

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Control (N = 22)</th>
<th>All demented (N = 23)</th>
<th>AD (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate word recognition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity index</td>
<td>0.67</td>
<td>0.22****</td>
<td>0.02****</td>
</tr>
<tr>
<td>0–1</td>
<td>–0.55–0.76</td>
<td>–0.55–0.3</td>
<td></td>
</tr>
<tr>
<td>Reaction time (msec)</td>
<td>1724</td>
<td>5237****</td>
<td>5789**</td>
</tr>
<tr>
<td>848–3336</td>
<td>1291–18541</td>
<td>1291–18541</td>
<td></td>
</tr>
<tr>
<td><strong>Delayed word recognition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity index</td>
<td>0.63</td>
<td>0.27***</td>
<td>0.14***</td>
</tr>
<tr>
<td>0–0.92</td>
<td>–0.44–0.92</td>
<td>–0.19–0.67</td>
<td></td>
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<tr>
<td>Reaction time (msec)</td>
<td>1423</td>
<td>3715****</td>
<td>4951***</td>
</tr>
<tr>
<td>827–2247</td>
<td>1060–12984</td>
<td>1392–12984</td>
<td></td>
</tr>
<tr>
<td><strong>Delayed picture recognition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity index</td>
<td>0.85</td>
<td>0.36****</td>
<td>0.12****</td>
</tr>
<tr>
<td>0.57–1.0</td>
<td>–0.37–0.86</td>
<td>–0.37–0.61</td>
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<tr>
<td>Reaction time (msec)</td>
<td>1278</td>
<td>3616****</td>
<td>5248**</td>
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<tr>
<td>789–2027</td>
<td>1123–12206</td>
<td>1123–12206</td>
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<tr>
<td><strong>Memory scanning task</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity index</td>
<td>0.67</td>
<td>0.19***</td>
<td>0.07**</td>
</tr>
<tr>
<td>–0.22–1.0</td>
<td>–0.19–1.0</td>
<td>–0.19–0.55</td>
<td></td>
</tr>
<tr>
<td>Reaction time (msec)</td>
<td>1311</td>
<td>3872****</td>
<td>4515***</td>
</tr>
<tr>
<td>643–2151</td>
<td>1311–10451</td>
<td>1336–10451</td>
<td></td>
</tr>
<tr>
<td><strong>Choice reaction task</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time (msec)</td>
<td>785.8</td>
<td>2035***</td>
<td>2869**</td>
</tr>
<tr>
<td>371–1487</td>
<td>573–11289</td>
<td>822–11289</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001.
## Test-retest reliability

Table 4. Test–retest reliability coefficients of the various measures of COGDRAS-D

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>r</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Immediate word recognition</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sensitivity</td>
<td>26</td>
<td>0.84</td>
<td>0.0001</td>
</tr>
<tr>
<td>Reaction time</td>
<td>26</td>
<td>0.83</td>
<td>0.0001</td>
</tr>
<tr>
<td>Delayed word recognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>26</td>
<td>0.65</td>
<td>0.0003</td>
</tr>
<tr>
<td>Reaction time</td>
<td>26</td>
<td>0.86</td>
<td>0.0001</td>
</tr>
<tr>
<td>Delayed picture recognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>26</td>
<td>0.81</td>
<td>0.0001</td>
</tr>
<tr>
<td>Reaction time</td>
<td>26</td>
<td>0.88</td>
<td>0.0001</td>
</tr>
<tr>
<td>Memory scanning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>24</td>
<td>0.53</td>
<td>0.0079</td>
</tr>
<tr>
<td>Reaction time</td>
<td>24</td>
<td>0.76</td>
<td>0.0001</td>
</tr>
<tr>
<td>Choice reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>26</td>
<td>0.93</td>
<td>0.0001</td>
</tr>
<tr>
<td>Number vigilance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% correct</td>
<td>25</td>
<td>0.75</td>
<td>0.0001</td>
</tr>
<tr>
<td>Reaction time</td>
<td>23</td>
<td>0.86</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Early work in Memory Clinics 2: Hammersmith Hospital Memory Clinic

THE COGNITIVE DRUG RESEARCH COMPUTERIZED ASSESSMENT SYSTEM IN THE EVALUATION OF EARLY DEMENTIA—IS SPEED OF THE ESSENCE?

CLAIRE G. NICHOLL
Senior Lecturer in Medicine, Division of Geriatric Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK

SEAN LYNCH
Lecturer, Psychiatry of Old Age, St Mary’s Hospital Medical School, London, UK

CORNELIUS A. KELLY
Senior Registrar, Psychiatry of Old Age, St Mary’s Hospital, London, UK

LINDA WHITE,* PAULINE M. SIMPSON† AND KEITH A. WESNES†
*Senior Researcher, †Research Director, Cognitive Drug Research Limited, Priory Court, Reading, UK

BRICE M. N. PITT
Professor, Psychiatry of Old Age, St Mary’s Hospital Medical School & Royal Postgraduate Medical School, Department of Medicine, Hammersmith Hospital, London, UK
Data showing ability of tests to identify deficits in MCI patients

- 98 of 99 patients able to perform tests
- Data showed that MCI patients had marked slowings of cognitive speed.
- The following patient groups could be reliably distinguished using the system:
  - worried well
  - Depressed
  - MCI
  - dementia
Early work in Memory Clinics 3: Memory Disorders Clinic
Institute of Mental Health Research
Canada

- Aim of study:
  - to determine how well traditional and automated tests could identify and differentiate Alzheimer’s disease from Huntington’s disease

**Canonical Discriminant Analysis:**

% subjects correctly identified

<table>
<thead>
<tr>
<th>Test</th>
<th>NC</th>
<th>AD</th>
<th>HD</th>
<th>Total</th>
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<tbody>
<tr>
<td>Mattis DRS</td>
<td>87%</td>
<td>67%</td>
<td>60%</td>
<td>71%</td>
</tr>
<tr>
<td>Folstein MMSE</td>
<td>80%</td>
<td>60%</td>
<td>61%</td>
<td>67%</td>
</tr>
<tr>
<td>Wechsler MS-R</td>
<td>77%</td>
<td>62%</td>
<td>62%</td>
<td>67%</td>
</tr>
<tr>
<td>ADAS</td>
<td>86%</td>
<td>67%</td>
<td>43%</td>
<td>65%</td>
</tr>
<tr>
<td>CDR</td>
<td>87%</td>
<td>77%</td>
<td>86%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Mohr E, Walker D, Randolph C, Sampson M, Mendis T
Utility of Clinical Trial Batteries in the Measurement of Alzheimer’s and Huntington’s Dementia *International Psychogeriatrics* 8: 397-411, 1996
Objective Psychometric Tests in Clinical Trials of Dementia Drugs

Position Paper from the International Working Group on Harmonization of Dementia Drug Guidelines

Steven H. Ferris, *Ugo Lucca, †Richard Mohs, ‡Bruno Dubois, §Keith Wesnes, ¶Hellmut Erzigkeit, #David Geldmacher, and **Neil Bodick

NYU Medical Center, New York, New York, U.S.A.; *Instituto “Mario Negri,” Milan, Italy; †Mount Sinai School of Medicine New York, New York, U.S.A.; ‡Groupe Hospitalier, Paris, France; §Cognitive Drug Research, Ltd., Reading, U.K.; ¶Universitat Erlangen–Nurnberg, Erlangen, Germany; #University Hospitals, Cleveland, Ohio, U.S.A.; and **Eli Lilly and Co., Indianapolis, Indiana, U.S.A.
site staff members. The Work Group concluded that computerized procedures initially should be used together with the established procedures in the field (e.g., the ADAS) so that the comparable utility and sensitivity of the two types of testing can be identified. If clear advantages of computerized procedures are demonstrated, such procedures might supersede existing methods.
Cognitive Domains That Should Be Assessed

The Work Group also achieved a consensus regarding the domains of cognitive function that ideally should be included in a comprehensive cognitive battery for AD trials. The recommended domains include memory, attention, processing speed, visuospatial function, praxis, language, executive function, and abstraction.
# Relationship between CDR factor scores and ADAS-cog

<table>
<thead>
<tr>
<th>CDR Factor Score</th>
<th>ADAS-Cog</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Quality of Memory</td>
<td>-0.766</td>
</tr>
<tr>
<td>Speed of Memory</td>
<td>0.381</td>
</tr>
<tr>
<td>Continuity of Attention</td>
<td>-0.406</td>
</tr>
<tr>
<td>Power of Attention</td>
<td>0.094</td>
</tr>
</tbody>
</table>

Test-Retest reliability for 774 Alzheimer’s patients tested 5 times over 26 weeks

<table>
<thead>
<tr>
<th></th>
<th>WEEKS 0 to 2</th>
<th>WEEKS 2 to 6</th>
<th>WEEKS 6 to 16</th>
<th>WEEKS 16 to 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power of Attention</td>
<td>0.86</td>
<td>0.86</td>
<td>0.82</td>
<td>0.83</td>
</tr>
<tr>
<td>Continuity of Attention</td>
<td>0.78</td>
<td>0.79</td>
<td>0.76</td>
<td>0.74</td>
</tr>
<tr>
<td>Quality of Episodic Memory</td>
<td>0.76</td>
<td>0.77</td>
<td>0.77</td>
<td>0.76</td>
</tr>
<tr>
<td>Speed of Memory</td>
<td>0.89</td>
<td>0.91</td>
<td>0.89</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Ability to detect Alzheimer’s disease progression related impairments in 170 patients randomised to placebo over 26 weeks.

Established Drug Sensitivity

- Alzheimer’s disease
  - Aricept
  - Galantamine
  - Velnacrine
  - Tacrine
  - S-12024
  - NS2330

- DLB
  - Rivastigmine
  - Aricept
  - Galantamine

- PDD
  - Aricept
  - Rivastigmine
Effects of Galanthamine in AD Phase IIA Study, n=30

Clinical Effect Size of attentional benefits of Galanthamine in AD

Choice Reaction Time

ORIGINAL ARTICLE

Early onset effects of galantamine treatment on attention in patients with Alzheimer’s disease

Bruno Vellas\textsuperscript{a}, Luís Cunha\textsuperscript{b}, Hermann-Josef Gertz\textsuperscript{c}, Peter Paul De Deyn\textsuperscript{d}, Keith Wesnes\textsuperscript{e}, Gerry Hammond\textsuperscript{f} and Susanne Schwalen\textsuperscript{g} on Behalf of the GAL-INT-28 Study Group
Study shows attention as assessed by CRT improves as time required by caregivers to tend to patients decreases.

Figure 2. Mean Choice Reaction Time (CRT: computerized test of patient attention) and time spent by caregivers assisting patients over time (asterisks indicate statistically significant improvement from baseline for both measures).
Study shows that both carers and patients report improvements in levels of attention.

*Figure 4. Caregivers' and patients' impression of patients' levels of attention (last bar shows patients' impressions at study endpoint, other bars represent caregivers' impressions)*
Parkinson’s Disease (PD), Parkinson’s Dementia (PDD) & Dementia with Lewy Bodies (DLB)
Dementia with Lewy bodies

Ian McKeith, Jacobo Mintzer, Dag Aarsland, David Burn, Helen Chiu, Jiska Cohen-Mansfield, Dennis Dickson, Bruno Dubois, John E Duda, Howard Feldman, Serge Gauthier, Glenda Halliday, Brian Lawlor, Carol Lippa, Oscar L Lopez, João Carlos Machado, John O'Brien, Jeremy Playfer, and Wayne Reid on behalf of the International Psychogeriatric Association Expert Meeting on DLB

Virtually unrecognised 20 years ago, DLB could within this decade be one of the most treatable neurodegenerative disorders of late life.
Consensus guidelines for the clinical diagnosis of probable and possible DLB:

Central features
Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment does not necessarily occur in the early stages but is evident with progression in most cases. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability can be especially prominent.

Core features (two core features essential for a diagnosis of probable, one for possible, DLB)
- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well formed and detailed
- Spontaneous features of parkinsonism

Outcome measures
Specific measures of attention and cognitive fluctuation, which are both part of the clinical profile of DLB and PDD, are sensitive to response to treatment intervention. Other key domains of executive functioning, visual perception, and memory systems must also be measured. The most
Pathological Causes of Dementia in Old Age

- Alzheimer's Disease: 50%
- Dementia with Lewy Bodies: 20%
- Mixed Alzheimer's/Vascular Disease: 10%
- Vascula. Disease: 10%
- Other Causes: 10%

After Perry R et al., 1989, 1990
Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study

Ian McKeith, Teodoro Del Ser, PierFranco Spano, Murat Emre, Keith Wesnes, Ravi Anand, Ana Cicin-Sain, Roberto Ferrara, René Spiegel

Summary

Background Dementia with Lewy bodies is a common form of dementia in the elderly, characterised clinically by fluctuating cognitive impairment, attention deficits, visual hallucinations, parkinsonism, and other neuropsychiatric features. Neuroleptic medication can provoke severe sensitivity reactions in patients with dementia of this type. Many deficits in cholinergic

Interpretation Rivastigmine 6–12 mg daily produces statistically and clinically significant behavioural effects in patients with Lewy-body dementia, and seems safe and well tolerated if titrated individually.

See Commentary page 2024
Primary Outcomes: Combined speed scores from CDR system & NPI

Figure 2: Computerised cognitive assessment system speed score: mean change (95% CIs) from baseline
“The clinical relevance of these improvements in attention was captured in caregiver reports of patients, describing them as more alert and switched on, and emphasised by reduced apathy scores on NPI” (p. 2035).

• “The use of reaction times as a second primary outcome measure is another novel feature of this trial.”
• “Neuropsychological functions other than those evaluated with the ADAS-Cog, … are also relevant to the treatment of patients with dementia”.
• McKeith and coworkers show that other features, such as neuropsychological symptoms and reaction times, can be meaningful outcome measures in dementia drug trials.”
Effects of rivastigmine on attention in DLB


<table>
<thead>
<tr>
<th>Power of Attention Factor</th>
<th>Improvemen over Pre-Dose (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Group</td>
<td>Rivastigmine Group</td>
</tr>
<tr>
<td>Pre-Dose</td>
<td>-200</td>
</tr>
<tr>
<td>Week 12</td>
<td>-600</td>
</tr>
<tr>
<td>Week 20</td>
<td>0</td>
</tr>
<tr>
<td>Week 23</td>
<td>200</td>
</tr>
</tbody>
</table>

Placebo Group
Rivastigmine Group

[Graph showing improvements over pre-dose (msec) for Placebo and Rivastigmine groups across different weeks.]
Effects of rivastigmine on memory in DLB

Overall Quality of Memory

1998 Pfizer Psychiatry Research Prize Winner


Cognitive Fluctuation illustrated by CRT profiles across 90 second trial for two subjects with different Clinical FC scores

Fluctuations in attention
PD dementia vs DLB with parkinsonism

C.G. Ballard, MRCPsych, MD; D. Aarsland, MD; I. McKeith, FRCPsych, MD; J. O’Brien, MRCPsych, DM; A. Gray, PhD; F. Cormack, BSc; D. Burn, MRCP, MD; T. Cassidy, MRCP; R. Starfeldt, BSc; J.-P. Larsen, MD; R. Brown, PhD; and M. Tovee, PhD

Abstract—Background: Marked impairments in and fluctuation of attention are characteristic of dementia with Lewy bodies (DLB). The comparative impairment of these cognitive domains in PD and PD dementia (PD dementia) has not been studied, and is important to the conceptual understanding of parkinsonian dementias. Method: Detailed evaluations of attention and fluctuating attention (Cognitive Drug Research computerized battery) were undertaken in 278 subjects (50 DLB, 48 PD dementia, 50 PD, 80 AD, 50 elderly controls) from the Newcastle dementia register and the Stavanger PD register (controls, PD, and PD dementia patients were recruited from both centers). DLB, AD, PD, and PD dementia were diagnosed using operationalized criteria. Results: Impairments in reaction time, vigilance, and fluctuating attention were comparable in patients with DLB and PD dementia, but were less substantially impaired in patients with DLB without parkinsonism. Patients with PD had significantly greater impairment of cognitive reaction time than elderly controls, and comparable impairments of cognitive reaction time to patients with AD. Patients with PD, however, did not exhibit fluctuation of attention. Conclusion: The profile of attentional impairments and fluctuating attention is similar in PD dementia and DLB with parkinsonism. The current findings do not support the current arbitrary distinctions between these patient groups. Importantly, patients with PD do not experience fluctuating attention.

NEUROLOGY 2002;59:1714–1720
Impairments to both cognitive reaction time and fluctuations (response variability) are shown to be hallmarks of PDD and DLB.

Use of cognitive data alone to identify and differentiate dementias

Use of CRT Variability data to differentiate dementias

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>AD - DLB</td>
<td>81%</td>
<td>92%</td>
</tr>
<tr>
<td>DLB - VaD</td>
<td>81%</td>
<td>82%</td>
</tr>
<tr>
<td>VaD - AD</td>
<td>64%</td>
<td>77%</td>
</tr>
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</table>


Ability of model to predict type of dementia from CDR data alone

Dementia associated with Parkinson’s disease


Murat Emre

Panel 2. Clinical features of dementia associated with PD

- Impaired attention with fluctuations
- Impaired executive functions
  - Concept formation
  - Problem solving
  - Set elaboration, shifting, and maintenance
  - Internally cued behaviour; benefit from external cues
- Impaired memory
  - Impaired free recall; benefit from external cues
  - Well preserved recognition
Attention and memory
Attention was found to be impaired in demented patients with PD, as shown by measures of attention such as cognitive reaction time and vigilance. There was also evidence for fluctuations in attention similar to those found in patients with dementia with Lewy bodies.
Rivastigmine for Dementia Associated with Parkinson’s Disease

CONCLUSIONS
In this placebo-controlled study, rivastigmine was associated with moderate improvements in dementia associated with Parkinson’s disease but also with higher rates of nausea, vomiting, and tremor.
<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Baseline Score</th>
<th>Change at Week 24</th>
<th>Between-Group Difference at Week 24</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean ±SD</td>
<td></td>
<td>Value</td>
</tr>
<tr>
<td><strong>Primary efficacy variables</strong></td>
<td></td>
<td></td>
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<tr>
<td>ADAS-cog score</td>
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<tr>
<td>Rivastigmine</td>
<td>329</td>
<td>23.8±10.2</td>
<td>−2.1±8.2</td>
<td>2.90†</td>
</tr>
<tr>
<td>Placebo</td>
<td>161</td>
<td>24.3±10.5</td>
<td>0.7±7.5</td>
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<tr>
<td>ADCS-CGIC score</td>
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<td>Rivastigmine</td>
<td>329</td>
<td>—</td>
<td>3.8±1.4</td>
<td>0.5</td>
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<tr>
<td>Placebo</td>
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<td>—</td>
<td>4.3±1.5</td>
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<tr>
<td><strong>Secondary efficacy variables</strong></td>
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<td>ADCS-ADL score</td>
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<tr>
<td>Rivastigmine</td>
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<td>41.6±18.6</td>
<td>−1.1±12.6</td>
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<tr>
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<td>41.2±17.7</td>
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<td>NPI-10 score</td>
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<td>12.7±11.7</td>
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<td>2.15†</td>
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<tr>
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<td>13.2±13.0</td>
<td>0.0±10.4</td>
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<td>MMSE score</td>
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<td>Rivastigmine</td>
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<td>19.5±3.8</td>
<td>0.8±3.8</td>
<td>1.00</td>
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<tr>
<td>Placebo</td>
<td>166</td>
<td>19.2±4.0</td>
<td>−0.2±3.5</td>
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<tr>
<td>CDR power of attention tests (msec)</td>
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<td>Rivastigmine</td>
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<td>2197.0±1170.2</td>
<td>−31.0±989.8</td>
<td>294.84†</td>
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<td>Placebo</td>
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<td>2490.5±2314.8</td>
<td>142.7±1780.2</td>
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<tr>
<td>D-KEFS Verbal Fluency Test (total no. of correct responses)</td>
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<td>Rivastigmine</td>
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<td>13.9±9.5</td>
<td>1.7±6.8</td>
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<td>−1.1±6.4</td>
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<tr>
<td>Ten Point Clock-Drawing score</td>
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<tr>
<td>Rivastigmine</td>
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<td>3.4±3.7</td>
<td>0.5±2.5</td>
<td>1.10</td>
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<tr>
<td>Placebo</td>
<td>30</td>
<td>2.9±3.8</td>
<td>−0.6±2.4</td>
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</table>
The ADAS-cog is specifically designed to measure the cognitive deficits in patients with Alzheimer’s disease and may have underestimated the clinical improvement in patients with Parkinson’s disease dementia because of a lack of sensitivity to the impairments seen in these patients. In fact, some of the secondary measures used by Emre et al. that one would expect to be more sensitive, such as the Computerized Assessment System power of attention tests and the Verbal Fluency test, did show a more substantial improvement. Still, the overall
Benefits of rivastigmine on attention in dementia associated with Parkinson disease

Abstract—In a 24-week, randomized, double-blind, placebo-controlled, multicenter study of rivastigmine, 487 patients with dementia associated with Parkinson disease underwent assessment of attention on the Cognitive Drug Research computerized cognitive assessment system before dosing and 16 and 24 weeks later. Significant benefits of rivastigmine over placebo were seen on all aspects of attention assessed: sustained attention, focused attention, consistency of responding, and central processing speed.

NEUROLOGY 2005;65:1654–1656

K.A. Wesnes, PhD; I. McKeith, MD; C. Edgar, MSc; M. Emre, MD; and R. Lane, MD
Power of Attention
(means +/- 95% C.I.)

** p<0.01 versus placebo
Continuity of Attention
means +/- 95% C.I.

**Time of testing**
- Week 0
- Week 16
- Week 24

**Improvement over week 0 (units)**
- Placebo
- Rivastigmine

*** p<0.001 versus placebo
**** p<0.0001 versus placebo
Reaction Time Variability
(means +/- 95% C.I.)

Time of testing

- week 0
- week 16
- week 24

Improvement over week 0 (C.V. %)

- Placebo
- Rivastigmine

*** p<0.001 versus placebo
* p<0.05 versus placebo

Time of testing

- week 0
- week 16
- week 24
Cognitive Reaction Time (means +/- 95% C.I.)

- Placebo
- Rivastigmine

**** p<0.0001 versus placebo
Clinical relevance of attentional improvement with rivastigmine in PDD

The CDR normative database enables the degree of recovery to normality to be identified – the optimal clinical relevance.

Attentional deficits affect activities of daily living in dementia associated with PD

Kolbjorn Bronnick, Uwe Ehrt, Murat Emre, Peter P. De Deyn, Keith Wesnes, Sibel Tekin and Dag Aarsland

J. Neurol. Neurosurg. Psychiatry published online 26 Jun 2006;
doi:10.1136/jnnp.2006.093146
Results

• Three cognitive factors were identified, with one factor emerging as a measure of vigilance and focused attention. This factor predicted different aspects of ADL status even after controlling for motor functions and the other cognitive factors. The attention factor was the single strongest cognitive predictor of ADL status, matching the strength of the effects of motor functions on ADL-status.

Conclusion

• Impaired attention is an important determinant of ADL functions in PDD.
Aricept in PDD & DLB

Conclusions

• Age-related cognitive declines can be treated
• Control of blood pressure important
• Attention is a major casualty in stroke
• Memory clinics provide a valuable service but there are too few
• Attention is also important in all of the dementias
• DLB & PDD can now be treated