Translational Medicine for CNS Compounds is Alive and Well in Phase I: A Review of 30 Years Experience

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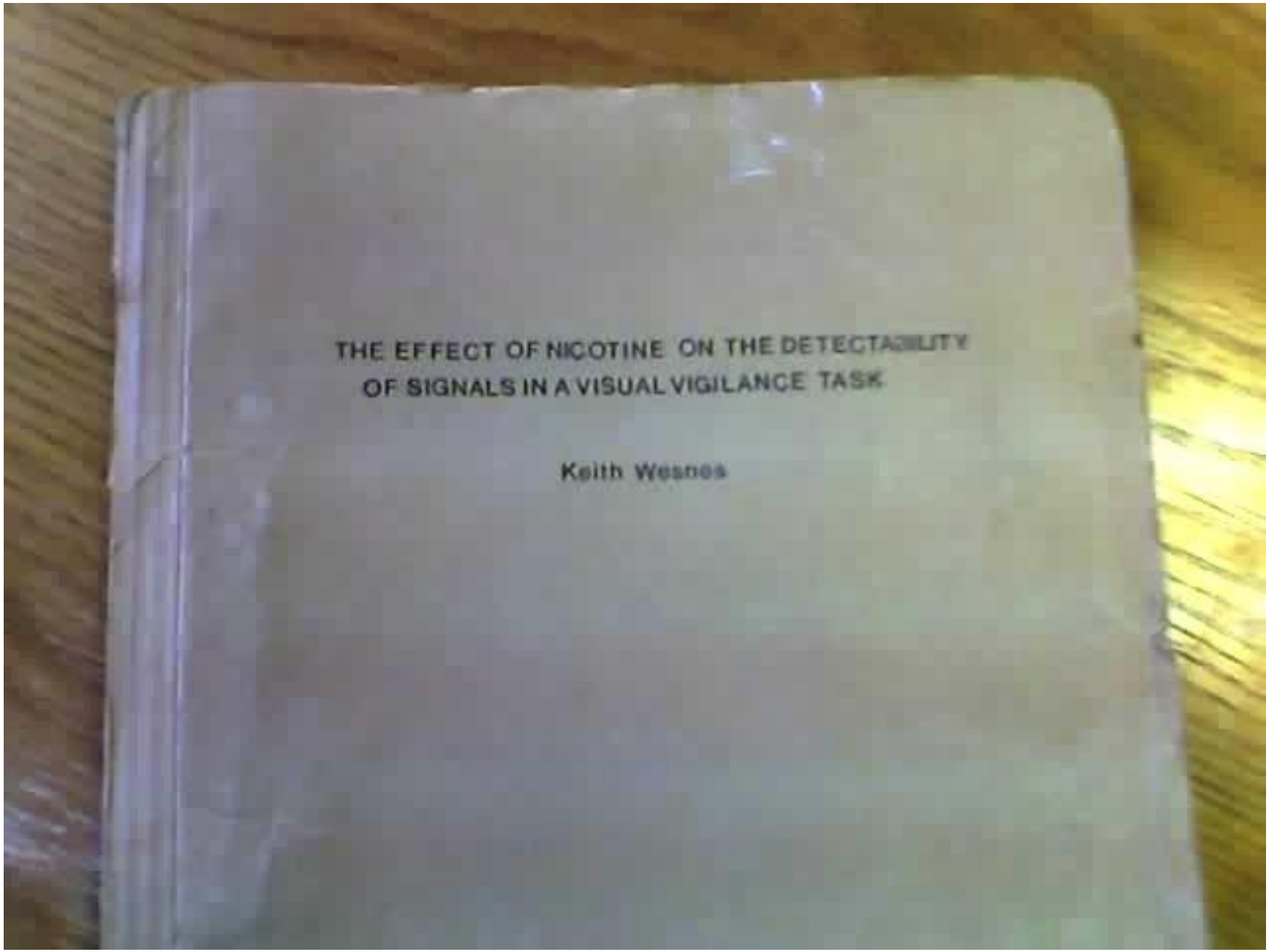
Undergraduate final year project 1972-1973

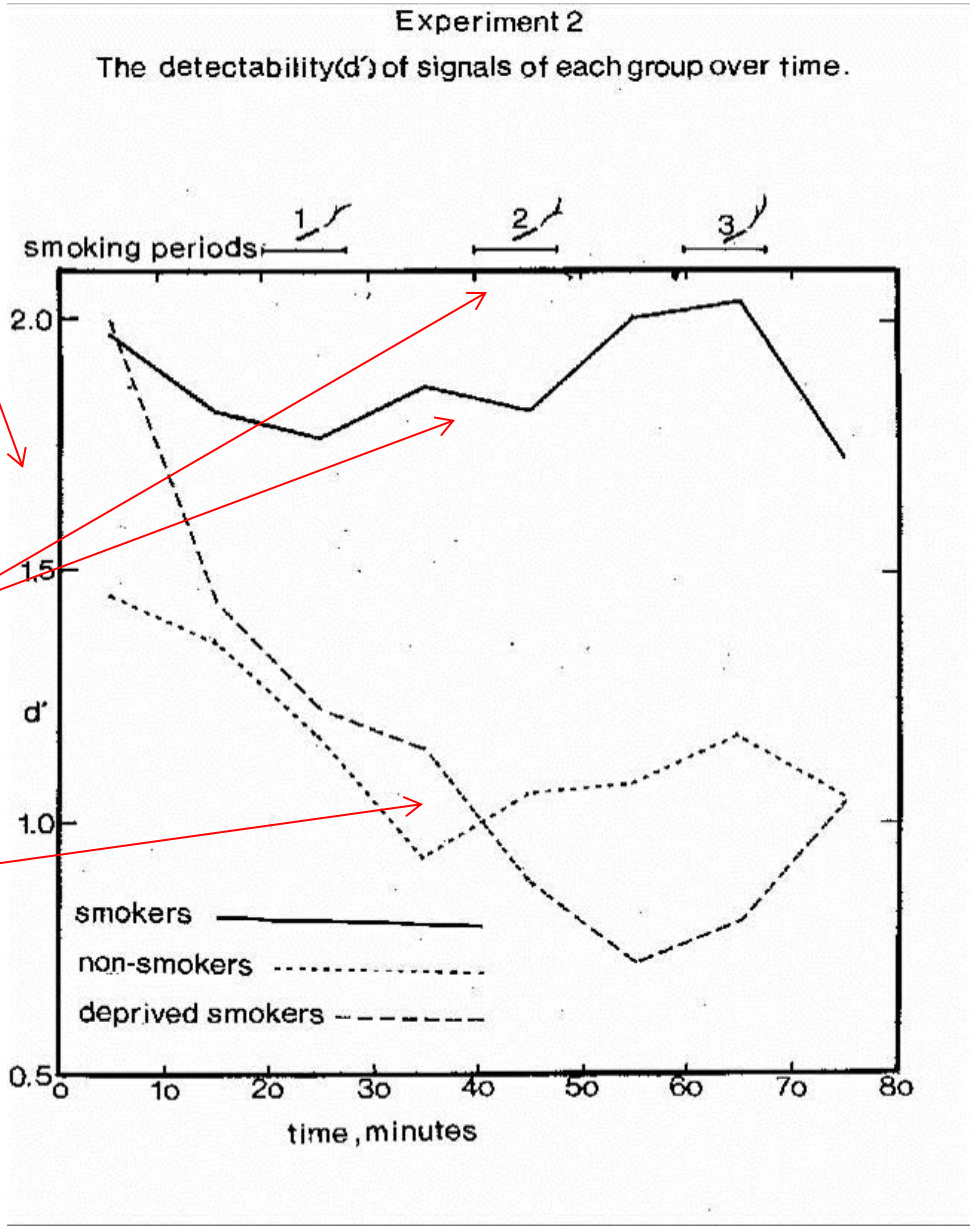


Study showed that smokers could better maintain concentration on a vigilance task

Higher scores mean better vigilance

Smokers who are allowed to smoke do well over time

Smokers who are not allowed to smoke & non smokers both do poorly over time



UNIVERSITY OF READING

THE EFFECTS OF NICOTINE AND SCOPOLAMINE ON HUMAN ATTENTION

KEITH WESNES

Psychopharmacology (1984) 82:147–150

Original investigations

Effects of scopolamine and nicotine on human rapid information processing performance

Keith Wesnes and David M. Warburton
Department of Psychology, University of Reading, Reading RG6 2AL, UK

One of the ten most cited clinical articles in first 40 years of *Psychopharmacology*

Miczek KA (2001) Landmark publications in Psychopharmacology: The first 40 years. Psychopharmacology 153: 399-401.

Journal of Psychopharmacology 11(3) (1997) 253–257
©1997 British Association for Psychopharmacology (ISSN 0269-8811)
SAGE Publications, London, Thousand Oaks, CA and New Delhi

Effect of haloperidol on nicotine-induced enhancement of vigilance in human subjects

C. Lee[1], S. Frangou[2], M. A. H. Russell[3] and J. A. Gray[1]

[1]*Departments of Psychology,* [2]*Psychiatry and the* [3]*National Addiction Centre, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.*

We posed the question whether the cognitive enhancement caused by nicotine in human subjects is mediated by dopamine (DA) release. This issue was addressed by testing performance in the Wesnes and Warburton vigilance task after s.c. nicotine with or without concomitant oral haloperidol. The subjects were moderate (10–14 cigarettes/day) smokers after overnight deprivation of smoking. After an initial practice session, each subject

Discussion

The improvement we observed in detection sensitivity (A') confirms the enhancement of vigilance performance reported previously in deprived smokers given nicotine (Wesnes and Warburton, 1978). Since we saw no change in the rate of false alarms, response bias (B') or reaction time, this effect of nicotine appears to constitute a genuine improvement in sensory selection and/or attention. We did not study non-

Psychopharmacology (1984) 84:5–11

Psychopharmacology
© Springer-Verlag 1984

The separate and combined effects of scopolamine and nicotine on human information processing

K. Wesnes and A. Revell

Department of Psychology, University of Reading, Reading RG6 2AL, UK

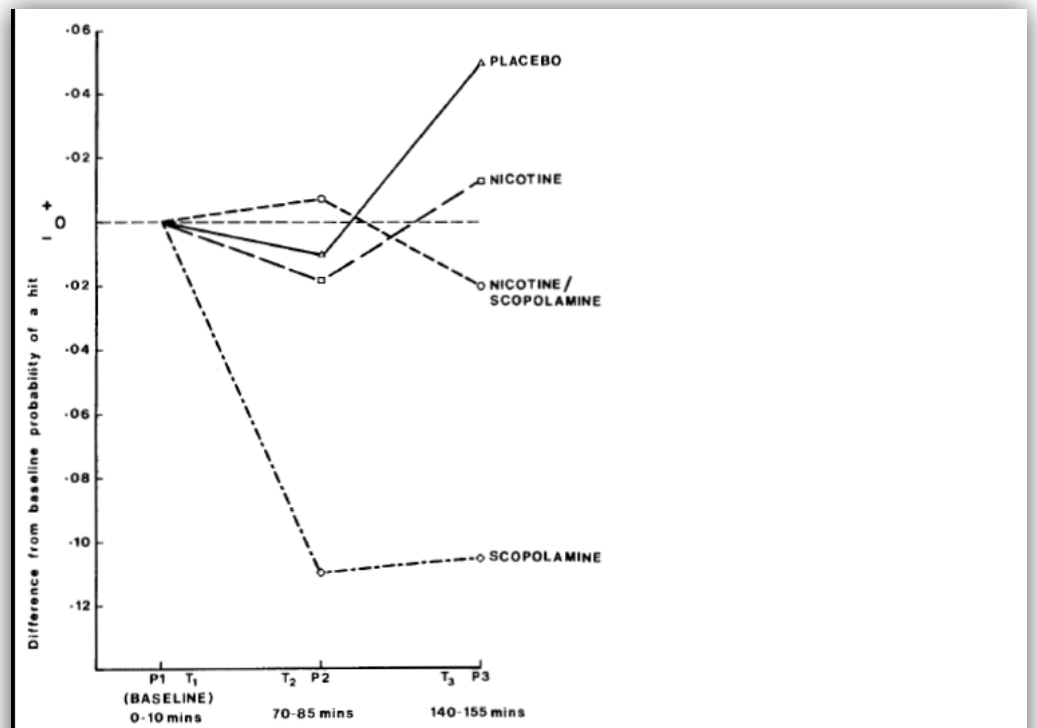


Fig. 1. The difference from baseline hit probabilities on the rapid information processing task under the four conditions of Experiment 2. See Table 3 for description of conditions

Nicotine treatment of mild cognitive impairment

A 6-month double-blind pilot clinical trial

P. Newhouse, MD
K. Kellar, PhD
P. Aisen, MD
H. White, MD
K. Wesnes, PhD

ABSTRACT

Objective: To preliminarily assess the safety and efficacy of transdermal nicotine therapy on cognitive performance and clinical status in subjects with mild cognitive impairment (MCI).

Methods: Nonsmoking subjects with amnestic MCI were randomized to transdermal nicotine (15 mg per day or placebo) for 6 months. Primary outcome variables were attentional improvement

Classification of evidence: This study provides Class I evidence that 6 months of transdermal nicotine (15 mg/day) improves cognitive test performance, but not clinical global impression of change, in nonsmoking subjects with amnestic MCI. *Neurology*® 2012;78:91-101

Correspondence & reprint requests to Dr. Newhouse: Paul.Newhouse@vanderbilt.edu

significant nicotine-induced improvement. There was no statistically significant effect on clinician-rated global improvement. The secondary outcome measures showed significant nicotine-associated improvements in attention, memory, and psychomotor speed, and improvements were seen in patient/informant ratings of cognitive impairment. Safety and tolerability for transdermal nicotine were excellent.

Conclusion: This study demonstrated that transdermal nicotine can be safely administered to nonsmoking subjects with MCI over 6 months with improvement in primary and secondary cognitive measures of attention, memory, and mental processing, but not in ratings of clinician-rated global impression. We conclude that this initial study provides evidence for nicotine-induced cognitive improvement in subjects with MCI; however, whether these effects are clinically important will require larger studies.

Classification of evidence: This study provides Class I evidence that 6 months of transdermal nicotine (15 mg/day) improves cognitive test performance, but not clinical global impression of change, in nonsmoking subjects with amnestic MCI. *Neurology*® 2012;78:91-101

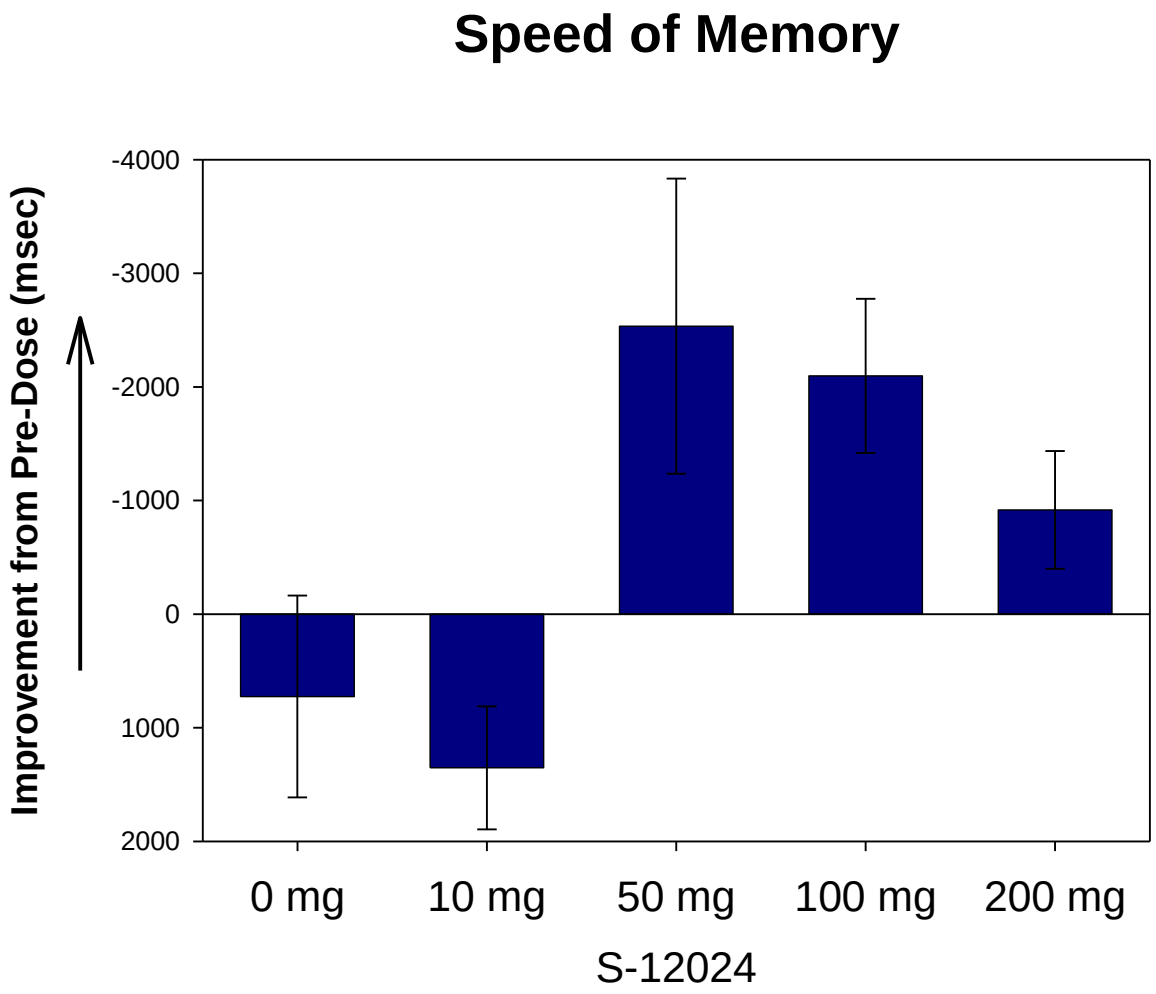
Case Study S-12024

S-12024 releases vasopressin, possibly via nicotinic mechanism

PHASE 1

- CDR testing added to multiple dosing safety and tolerability in elderly volunteers
- Inclusion of CDR testing identified a range of cognitive benefits.
- Data dose dependent, 50 and 100 mg doses most effective

Enhancement in cognitive function in Phase I with S-12024

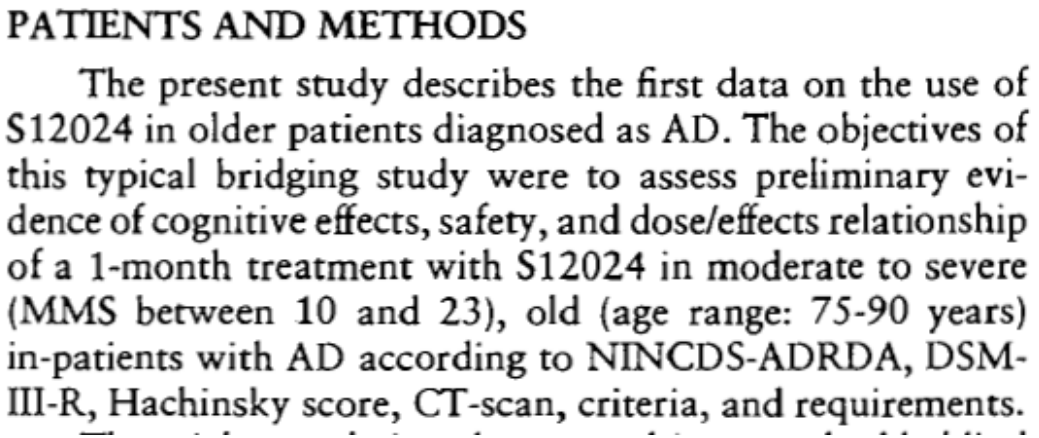


de Wilde HJG, Wesnes K, Neuman E, Malbezin M, Castagné I, Guez D, Crijns HJMJ, Jonkman JHG. (1995). Cognitive enhancing effects of S12024-2 during repeated oral administration at 4 dose levels in 36 healthy elderly volunteers. European Journal of Clinical Investigation 25, Suppl. 2: A65.

S-12024 Phase IIA

Phase I findings confirmed in 28 day follow up trial in Alzheimer's disease patients using CDR System

- Placebo controlled bridging trial conducted in 53 AD patients, MMSE 10 to 23 (1)
- Significant improvements seen to choice reaction time, digit vigilance speed and quality of episodic memory.



PATIENTS AND METHODS

The present study describes the first data on the use of S12024 in older patients diagnosed as AD. The objectives of this typical bridging study were to assess preliminary evidence of cognitive effects, safety, and dose/effects relationship of a 1-month treatment with S12024 in moderate to severe (MMS between 10 and 23), old (age range: 75-90 years) in-patients with AD according to NINCDS-ADRDA, DSM-III-R, Hachinsky score, CT-scan, criteria, and requirements.

1. Allain H, Neuman E, Malbezin M, Salzman V, Guez D, Wesnes K, Gandon JM (1997). Bridging study of S12024 in 53 in-patients with Alzheimer's disease. J Am Geriatr Soc. 45: 125-126.

S-12024 Phase III

Findings confirmed in 6 country study in 404 Alzheimer's patients

- 100 mg dose effective in AD patients with at least one APOE ϵ4 allele
- Effects include significant improvement on MMSE plus clinical interview based impression of change

Richard F, Helbecque N, Neuman E et al. (1997). APOE genotyping and response to drug treatment in Alzheimer's disease. Lancet, 349, 539.

CDR SYSTEM™
Computerized Cognitive Testing

α7

Case Study α7 Nicotinic Agonist GTS 21

- Can cognition enhancing effects of GTS-21 be seen in a Phase I multiple dosing trial?
- Ascending dose, parallel group design in 16 volunteers, 4 received placebo and 12 active dosing.

Neuropsychopharmacology (2003) 28, 542–551
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www.neuropsychopharmacology.org

Safety, Pharmacokinetics, and Effects on Cognitive Function of Multiple Doses of GTS-21 in Healthy, Male Volunteers

Harumi Kitagawa[1], Toshiharu Takenouchi[2], Ryotaro Azuma[3], Keith A Wesnes[4], William G Kramer[5], Donald E Clody[*,6] and Angela L Burnett[7]

[1]Quintiles, Inc., Tokyo, Japan; [2]Taiho Pharmaceutical Co. Ltd, Tokyo, Japan; [3]Taiho Pharmaceutical Co. Ltd, Tokushima, Japan; [4]Cognitive Drug Research; Reading, UK; [5]Kramer Consulting, LLC, North Potomac, MD, USA; [6]Quintiles, Inc., Cranford, NJ, USA; [7]Quintiles, Inc.; Rockville, MD, USA

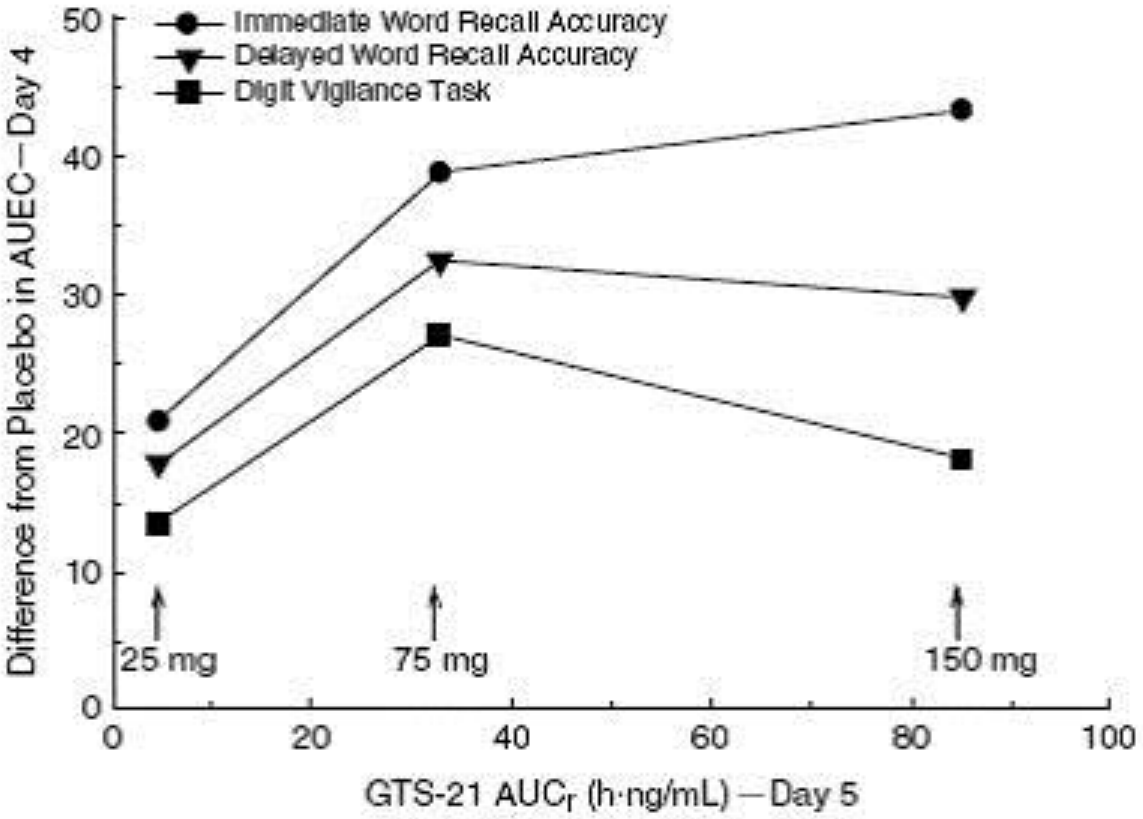


Figure 8 Relationship between the effects of GTS-21 on immediate and delayed word recall accuracy and digit vigilance (AUEC) and drug exposure (AUC).

Kitagawa H, Takenouchi T, Azuma R, Wesnes K, Kramer W, Clody DE, Burnett A. (2003). Safety, pharmacokinetics, and effects on cognitive function of multiple doses of GTS-21 in healthy male, volunteers. Neuropsychopharmacology 28: 542-551.

ORIGINAL ARTICLE

Proof-of-Concept Trial of an α7 Nicotinic Agonist in Schizophrenia

Ann Olincy, MD; Josette G. Harris, PhD; Lynn L. Johnson, PharmD; Vicki Pender, BS; Susan Kongs, BS; Diana Allensworth, BS; Jamey Ellis, BS; Gary O. Zerbe, PhD; Sherry Leonard, PhD; Karen E. Stevens, PhD; James O. Stevens, DVM, PhD; Laura Martin, MD; Lawrence E. Adler, MD; Ferenc Soti, PhD; William R. Kem, PhD; Robert Freedman, MD

GTS-21 (DMXB-A) improves attention in Schizophrenia: validating work in Phase I and confirming necessity to establish cognitive effects of nicotinics as early as possible in development

Results: Significant neurocognitive improvement was found on the Repeatable Battery for the Assessment of Neuropsychological Status total scale score, particularly for the lower DMXB-A dose compared with placebo. Effects were greater than those of nicotine in a similar study. Significant improvement in P50 inhibition also occurred. Patients generally tolerated the drug well.

Conclusions: An α7 nicotinic agonist appears to have positive effects on neurocognition in persons with schizophrenia. Longer trials are needed to determine the clinical utility of this novel treatment strategy.

Arch Gen Psychiatry. 2006;63:630-638

CNS Drug News

Issue No. 133 9th March 2006

Memory reports positive preliminary Phase I cognitive data for MEM 3454

Memory Pharmaceuticals has reported preliminary cognitive data from the multiple ascending-dose (MAD) study segment of the Phase I trial programme of MEM 3454, the company's lead drug candidate in its nicotinic alpha-7 agonist programme. Cognition data generated in this study, using the Cognitive Drug Research (CDR) battery demonstrated that a 15mg dose of MEM 3454, administered once daily for a period of 13 days, showed a statistically significant effect on the Quality of Episodic Secondary Memory (QESM), one of the study's primary efficacy variables.

This was a randomised, double-blind, placebo-controlled study of three doses of MEM 3454 (15, 50 and 150mg), and involved 48 healthy young male and female volunteers. The primary purpose of the study was to investigate the safety, tolerability and pharmacokinetics of MEM 3454 in healthy volunteers, while a secondary objective of the study was to assess the cognitive effects of the doses tested using the CDR battery.

In the study, after oral administration of MEM 3454 15mg once daily for 13 days, there was a statistically significant effect on the QESM of the healthy volunteers; this effect at 15mg is supported by Memory's preclinical work with MEM 3454. The other doses administered in the study did not show a similarly statistically significant effect, although there was a trend toward efficacy at the 50mg dose. Other domains in the CDR battery measure other cognitive effects such as psychomotor speed and attention, and while trends toward improvement were also seen on these domains at MEM 3454 15mg, the results were not as substantial as those obtained for the QESM domain.

CNS Drug News

Issue No. 174 15th November 2007

Memory reports positive Phase IIa results for MEM 3454 in AD

Memory Pharmaceuticals has reported positive top-line data from a proof-of-concept, Phase IIa trial of MEM 3454, its lead nicotinic alpha-7 receptor partial agonist, in 80 patients with mild-to-moderate Alzheimer's disease (AD) over an eight-week treatment period.

The primary endpoint was the change from baseline in QESM factor score. The CDR battery was administered at baseline and on six days during the treatment period, at four time points (pre-dosing and two, four and eight hours post-dosing) each day. For the eight-hour post-dose time points over the treatment period, subjects receiving MEM 3454 5 and 15mg demonstrated a statistically significant effect on the QESM compared to placebo (p=0.023 and p=0.05, respectively).

Secondary endpoints in the trial included other composite scores from the CDR battery that measure working memory, attention and executive function, plus the ADAS-Cog. On secondary CDR battery measures, using all time points combined over the treatment period, the 5 and 15mg doses achieved statistically significant positive results on Quality of Working Memory (p=0.031 and p=0.047). The 15mg group also demonstrated trends to efficacy on Speed of Memory (p=0.08). For the ADAS-Cog, the 15mg group showed numeric improvements favouring treatment over placebo. There

α4ß2

TC-1734: Summary of Tolerability and Efficacy

TARGACEPT

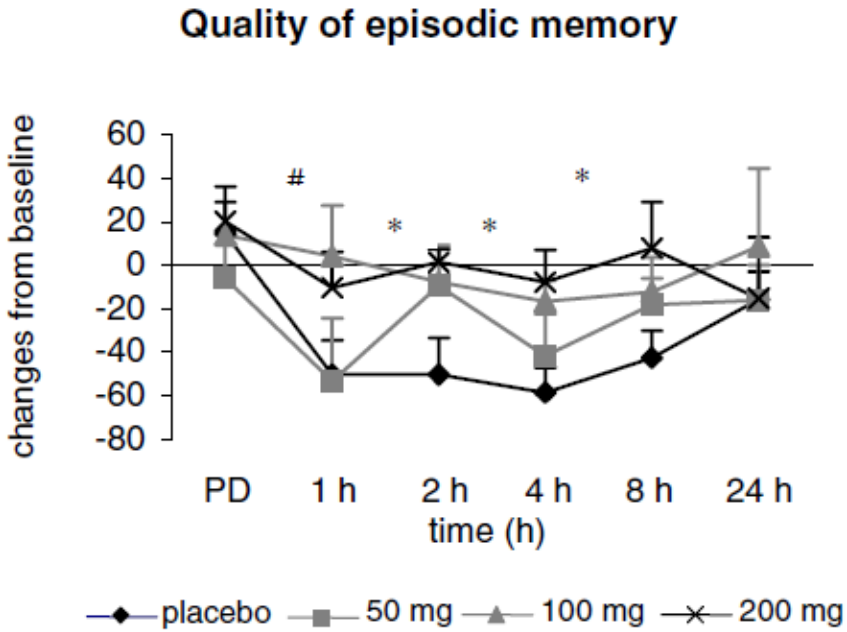
Design	Subjects/Dosing	Safe & Well Tolerated	Comments
Single Rising Dose	48 young adult males, 2-320mg	✓	Dose and concentration dependent acceleration of brain waves associated with attention
Multiple Rising Dose	24 young adult males, 50-200mg, 1x/day for 10 days	✓	Dose dependent positive effect of attention
Pharmacokinetic	6 elderly subjects, single 80mg dose	✓	Positive effects on memory (immediate and delayed word recall, and quality of episodic memory) lasting up to 48 hours
Phase 2a – AAMI Double blind, placebo-controlled, cross-over	76 subjects age 60+, 50, 100, 125 and 150mg dose groups, 1x/day	✓	Positive effects on 3 of 5 CDR factor scores
Phase 2a – MCI Double blind, placebo-controlled, cross-over	40 subjects age 60+, 50 and 100mg dose groups, 1x/day	✓	Positive signal on 3 of 5 CDR factor scores

Psychopharmacology (2007) 191:919–929
DOI 10.1007/s00213-006-0675-x

ORIGINAL INVESTIGATION

Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers

G. Dunbar · P. H. Boeijinga · A. Demazières · C. Cisterni · R. Kuchibhatla · K. Wesnes · R. Luthringer



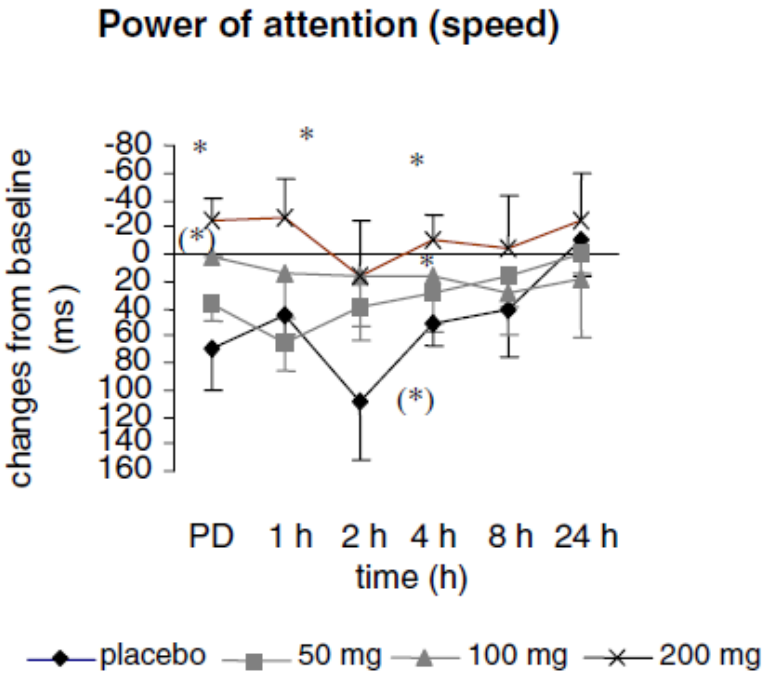


Fig. 1 Principal CDR tests showing significant changes by TC-1734 compared to placebo on day 10. Results are expressed as means (with standard error bars) on changes from baseline for placebo and each dose of TC-1734. *Asterisk* stands for statistical differences between dose 200 mg and placebo; *number sign* stands for statistical differences between dose 100 mg and placebo. (*), (#) $0.05<p<0.1$; *, #$p<0.05$, **$p<0.01$, (*)

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JMN (Online)ISSN 1559-1166
DOI 10.1385/JMN/30:1-2:169

ORIGINAL ARTICLE

Cognitive Enhancement in Man With Ispronicline, A Nicotinic Partial Agonist

Geoffrey C. Dunbar and Ramana Kuchibhatla*

Targacept, Inc., Winston Salem, NC 27101

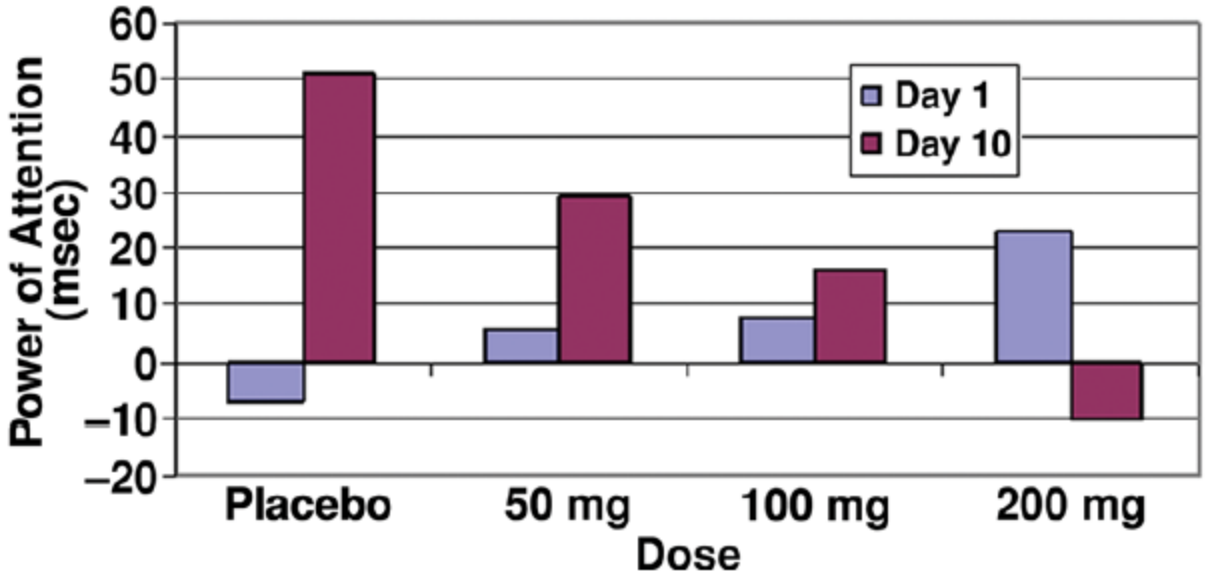

Fig. 1. Change in power of attention between days 1 and 10 with dose of ispronicline.

Benefits in elderly volunteers

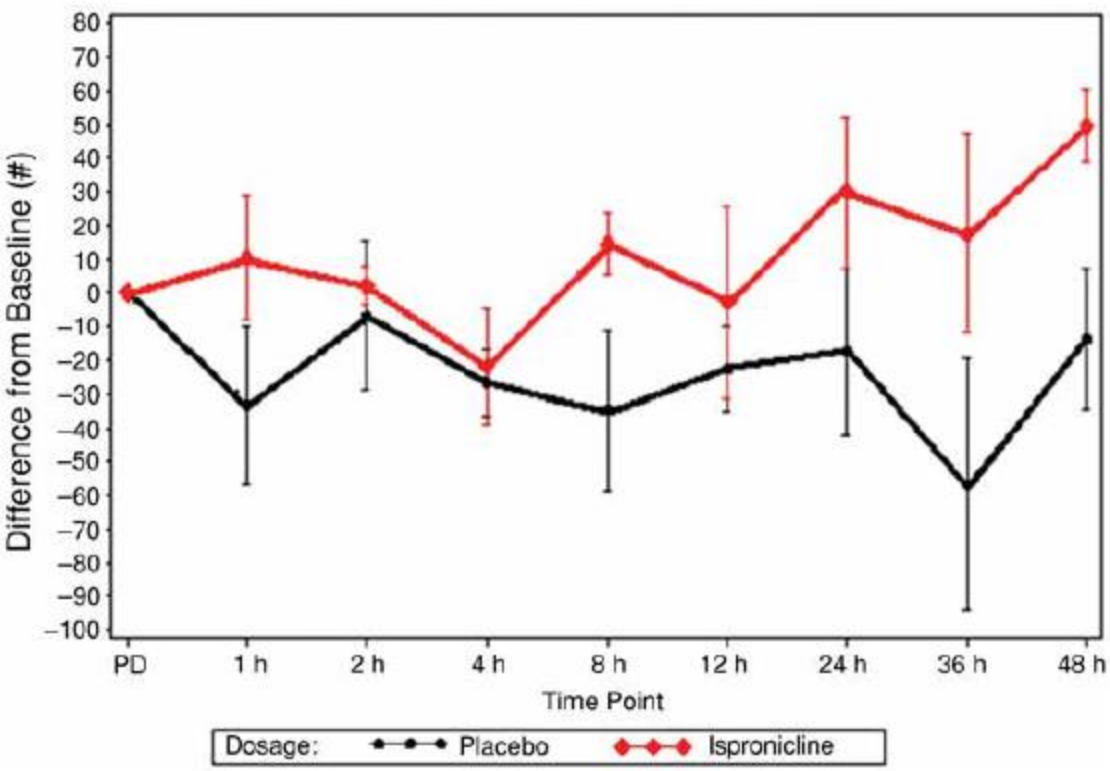

Fig. 2. Change in episodic memory following 80 mg ispronicline

Journal of Molecular Neuroscience

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J Psychopharmacol OnlineFirst, published on August 4, 2006 as doi:10.1177/0269881106066855

Original Papers

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10.1177/0269881106066855

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.*
Fraser Inglis *Glasgow Memory Clinic, Golden Jubilee National Hospital, Glasgow, UK.*
Ramana Kuchibhatla *Clinical Development and Regulatory Affairs, Targacept Inc., Winston Salem, USA.*
Tonmoy Sharma *Clinical Neuroscience Research Centre, Dartford, UK.*
Mark Tomlinson *Sequani Clinical, Ledbury, UK.*
James Wamsley *Clinical Development and Regulatory Affairs, Targacept Inc., Winston Salem, USA.*

Most consistent effects with lowest dose

Table 4 Group differences on CDR factor scores by ispronicline dose.

CDR factor	Oral ispronicline 50 mg (n=20)
Power of attention	Ispronicline p=0.001
Continuity of attention	Ispronicline p=0.001 *
Episodic memory	Ispronicline p=0.019 *
Working memory	
Speed of memory	Ispronicline p<0.01*

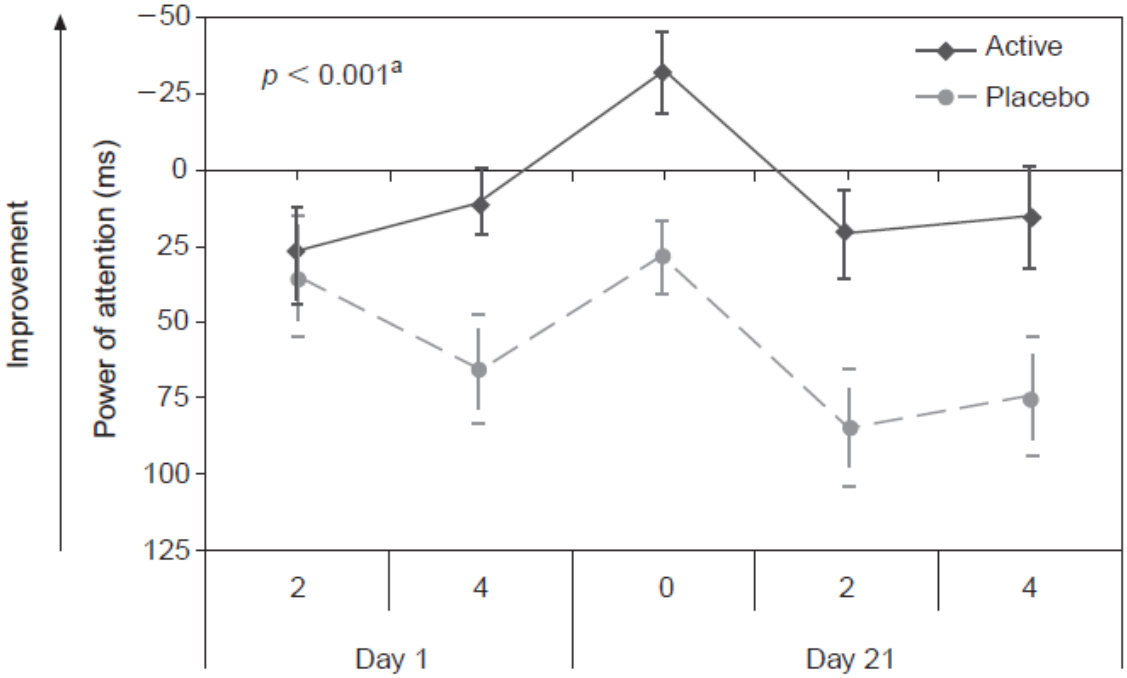

Figure 1 Results for the CDR factor power of attention change score, for ispronicline 50 mg, on day 1 (2 and 4 hours) and day 21 (0, 2 and 4 hours)

a = ANOVA p-value for both periods and all time points

Journal of Psychopharmacology
http://jop.sagepub.com

Abstracts

J Psychopharmacol 2006; 20; 108
DOI: 10.1177/1359786806066089

ISPRONICLINE, A NEURONAL NICOTINIC RECEPTOR PARTIAL AGONIST IN THE TREATMENT OF SUBJECTS WITH MILD COGNITIVE IMPAIRMENT

Dunbar G
Targacept Inc. 200 East First Street, Suite 300, Winston Salem, NC 27101, USA.

Objective: The present study assessed the safety, tolerability and effect on cognition of ispronicline 50 mg and 100 mg, in volunteers with MCI.

Background: Ispronicline is a partial agonist at the α4β2 neuronal nicotinic (acetylcholine) receptor that has demonstrated pro-cognitive and neuroprotective properties in multiple preclinical models. The compound is highly selective for this receptor, having no effect at muscle or ganglion receptors. Consequently the molecule minimizes peripheral side effects at doses that enhance cognition.

Methods: Volunteers aged >60 years with subjective memory impairment and who scored at least 1.5 standard deviations below that seen in age matched controls on the Wechsler Memory Scale-R, Paired Associate Learning Test, were randomized into a double-blind, placebo-controlled, cross-over study. Treatment was for 3 weeks with a 2-week washout between treatment periods. Separate cohorts of 20 volunteers were given 50 mg and 100 mg ispronicline in sequential order before breakfast. Cognitive performance was assessed using the Cognitive Drug Research (CDR) computerized test battery on days 1 and 21 of each treatment period at 0, 2 and 4 hours post-dosing. The 5 CDR factor scores were calculated using results from nine individual tasks.

Analysis was undertaken with the per protocol population using a Mixed Model Analysis of Variance. If a significant carry over effect occurred, only data from the first period of the cross-over were considered.

Results: Both doses of ispronicline demonstrated a favourable safety profile and were well tolerated. No effect of clinical significance was seen on biochemistry, haematological or urinary measures. Likewise no effect was seen on vital signs, ECG or Holter monitoring. The most common adverse event (AE) was light-headedness. Results for effect on cognition are given below. No effect was seen with 50 mg there being advantage for placebo on two factor scores. However, ispronicline 100 mg was superior to placebo on four of the five factors.

	CDR factor scores				
Ispronicline	Power of attention	Continuity of attention	Episodic memory	Working Memory	Speed of memory
50 mg				++	++
100 mg	##		##	#	#

Ispronicline ## – $p<0.05$, # – $p<0.1$ Placebo ++ – $p<0.05$

Conclusions: Both 50 and 100 mg of ispronicline demonstrated a favourable safety profile and were well tolerated. The most common AE was light-headedness. Considering impact on cognition, 100 mg was the most effective dose.

Acknowledgement: Targacept Inc. would like to thank Dr Fraser Inglis (Clydebank), Dr Tonmoy Sharma (Dartford) and Dr Mark Tomlinson (Ledbury) for their help in recruiting volunteers into this study.

Phase I Effects of ABT-089 on unimpaired cognitive function

Results (continued)

Effects of ABT-089 on Cognitive Performance After a Single Dose (Day 1) and Chronic Dosing (Day 4)

- CDR:
  - Day 1: No robust findings were observed on Day 1 for ABT-089 on CDR composite scores
  - Day 4
    - Across dose groups, ABT-089 demonstrated a linear statistical trend ($P \leq 0.100$) for improvement on Power of Attention and demonstrated significantly improved cognitive performance ($P \leq 0.050$) on Spatial Working Memory
    - ABT-089 15 mg QD and 40 mg QD significantly improved ($P \leq 0.050$) performance on Speed of Memory at several time points
- CogState
  - No robust findings were observed on Day 1 or 4 for ABT-089 on CogState tasks

Baker J, Lenz R, Locke C, Wesnes K, Maruff P, Abi-Saab Q, Saltarelli M (2009). ABT-089, a neuronal nicotinic receptor partial agonist, reverses scopolamine-induced cognitive deficits in healthy normal subjects. Alzheimer's and Dementia 5: P325.

ABT-089, A Neuronal Nicotinic Receptor Partial Agonist, for the Treatment of Attention-Deficit/ Hyperactivity Disorder in Adults: Results of a Pilot Study

Timothy E. Wilens, Marleen H. Verlinden, Lenard A. Adler, Patricia J. Wozniak, and Scott A. West

Background: *This pilot study was designed to evaluate ABT-089, a neuronal nicotinic receptor partial agonist, as treatment for adult attention-deficit/hyperactivity disorder (ADHD).*

Methods: *Adults with ADHD received placebo, 2 mg, 4 mg, or 20 mg of ABT-089 for 2 weeks each in a randomized, double-blind, placebo-controlled, 4 × 4 Latin square design for a total of 8 weeks. In addition to the primary outcome, the Conner's Adult ADHD Rating Scale (CAARS), secondary rating scales, and neuropsychological and safety assessments were completed.*

Results: *A total of 11 adults with well-characterized ADHD completed this crossover study. ABT-089 b.i.d. was superior to placebo for the CAARS Total Symptom Score, which was the primary endpoint (placebo: 38.0 ± 1.9; 2 mg b.i.d.: 32.2 ± 1.9, one-tail* $p = .021$*; 4 mg b.i.d.: 33.2 ± 1.9,* $p = .047$*; 20 mg b.i.d.: 33.5 ± 1.9,* $p = .056$*). ABT-089 was also superior to placebo for the CAARS ADHD Index and Hyperactive/Impulsive scores and the Clinical Global Impression–ADHD Severity score. On the clinical efficacy endpoints, CAARS Total Symptom Score and CAARS Hyperactive/Impulsive score, a shallow inverted U-shaped dose–response curve was observed; however, the dose–response curve for attention and memory effects as measured by computerized cognitive testing seemed dose-linear. No clinically meaningful findings in safety assessments or side effect profile were observed.*

Conclusions: *Data from this pilot study suggest that ABT-089 might be effective in treating adult ADHD and that it is well tolerated. On the basis of these promising results, larger, parallel-group ABT-089 studies of longer duration are warranted.*

BIOL PSYCHIATRY 2006;59:1065–1070
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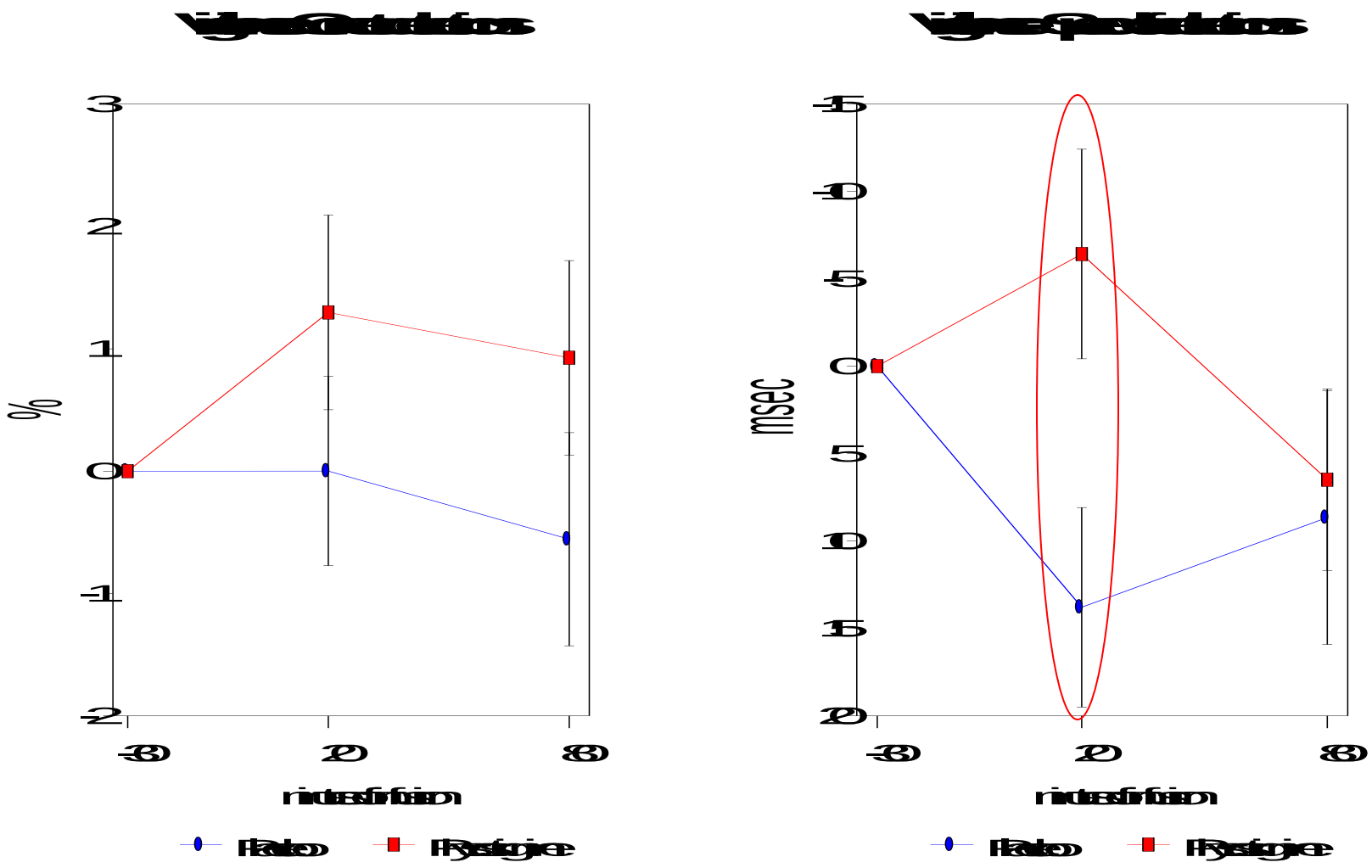
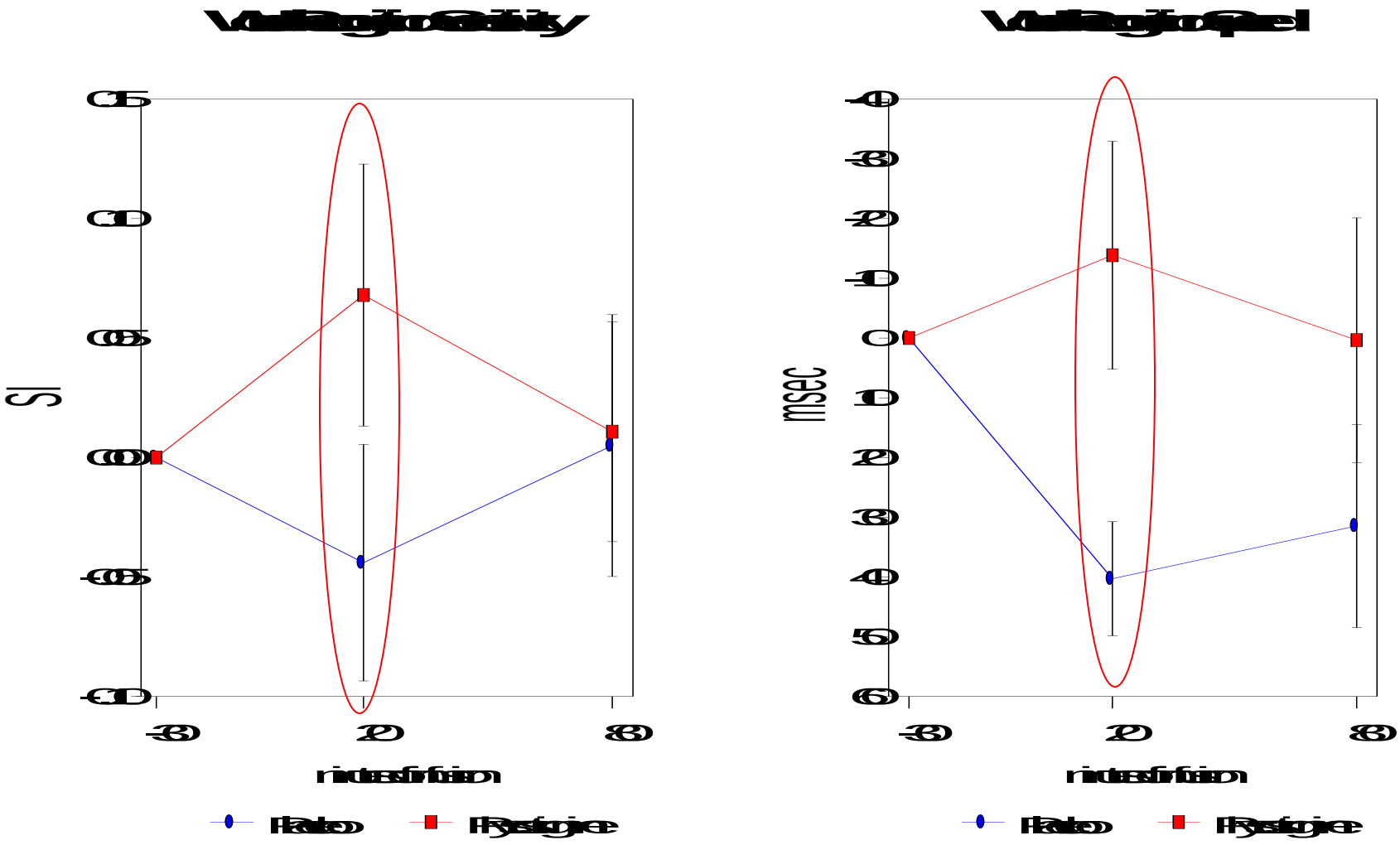
Cognition Enhancement



Wesnes KA, Simpson PM, Wallnöfer A, Dingemanse J, McClelland G, Malek N. (1994) Cognitive enhancement with physostigmine in young volunteers. Journal of Psychopharmacology 8 (Suppl).: A19.

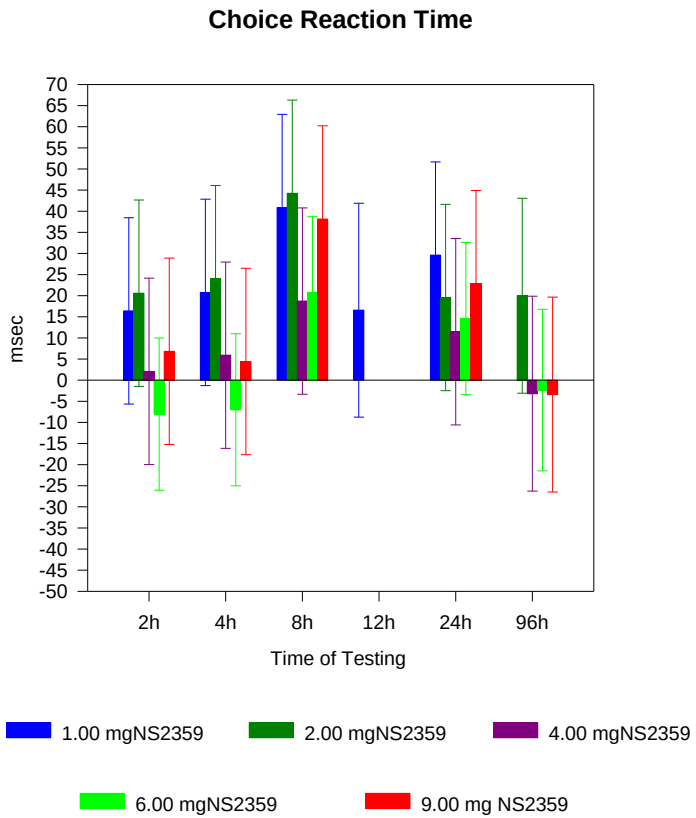


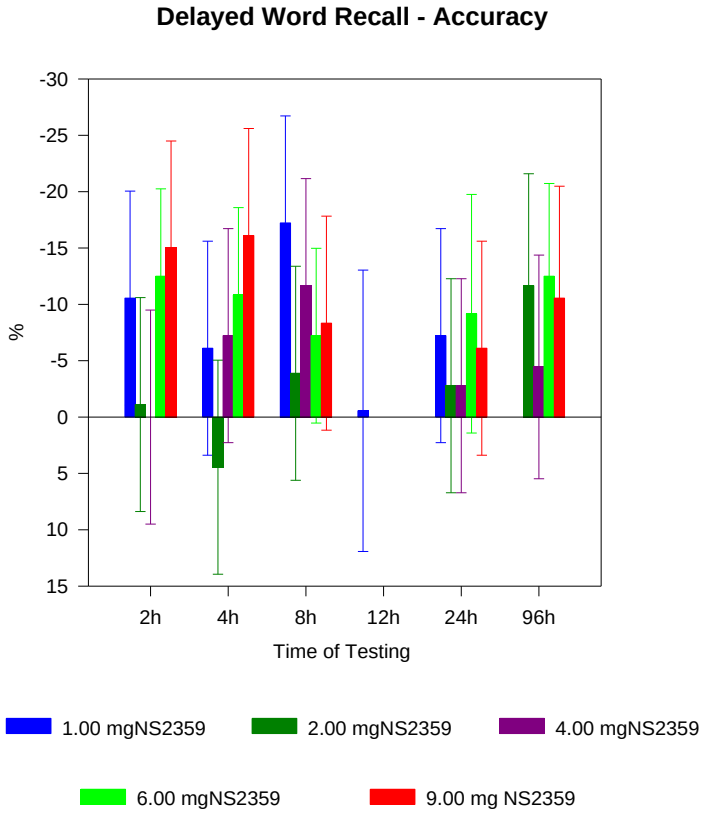
Wesnes KA, Simpson PM, Wallnöfer A, Dingemanse J, McClelland G, Malek N. (1994) Cognitive enhancement with physostigmine in young volunteers. Journal of Psychopharmacology 8 (Suppl).: A19.

Detecting Enhancement in Standard Phase I trials

- NS2359 studied in an ascending single dose safety and tolerability study in 56 healthy volunteers.
- The CDR System was administered at multiple time points during the study.
- CDR Tests of attention and verbal episodic memory were administered.
- The data on the following pages are changes from pre-dose expressed as differences from placebo.
- The graphs are plotted so that an ascending value represents and improvement.
- The bars represent mean changes with 95% confidence intervals, where the error bar does not cross the zero line, this dose is significantly superior to placebo.

Bosworth J, Jensen NO, Oliver S, Wesnes KA (1999) First cognitive effects of NS2359, a noradrenaline, dopamine & serotonin reuptake inhibitor, in volunteers. Journal of Psychopharmacology 13 (Suppl. A): A26.





Conclusion "NS2359 has clear cognition enhancing properties. These are evidenced by improvements to attention and an increased ability to retain verbal information in secondary memory".

Bosworth J, Jensen NO, Oliver S, Wesnes KA (1999) First cognitive effects of NS2359, a noradrenaline, dopamine & serotonin reuptake inhibitor, in volunteers. Journal of Psychopharmacology 13 (Suppl. A): A26.

Clinical trial with NS2359 in Adult ADHD

Behavioral and Brain Functions

BioMed Central

Research

Open Access

A randomized controlled trial of a novel mixed monoamine reuptake inhibitor in adults with ADHD

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Email: Timothy E Wilens* - twilens@partners.org; Thorsten Klint - TKLINT@PRDBE.JNJ.COM; Lenard Adler - lenard.adler@med.nyu.edu; Scott West - scott@cnshealthcare.com; Keith Wesnes - keithw@cognitivedrugresearch.com; Ole Graff - ole.x.graff@gsk.com; Birgit Mikkelsen - BOM@Neurosearch.dk

* Corresponding author

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Accepted: 13 June 2008

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Significant improvements to core CDR measures of attention and memory (n=95)

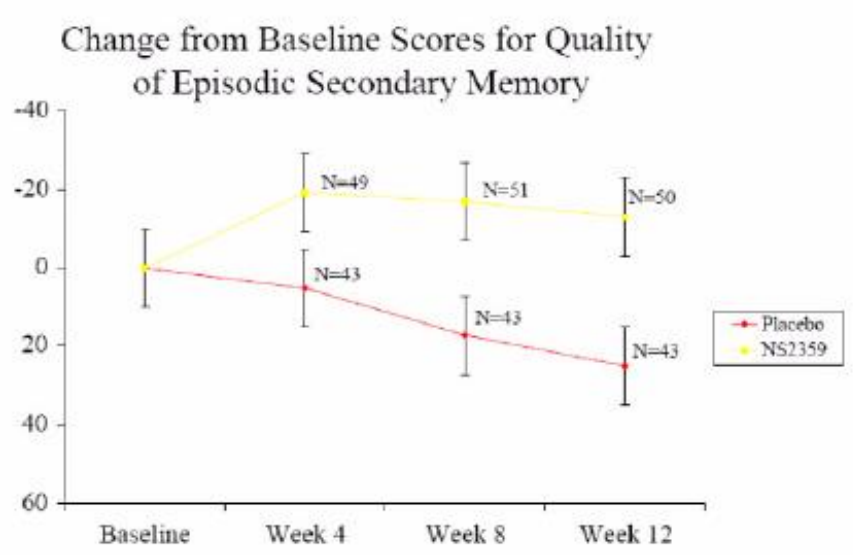


Figure 3
Change from baseline scores for Quality of Episodic Secondary Memory over the study period (Mean +/- SEM). Improvements from baseline are plotted to ascend.

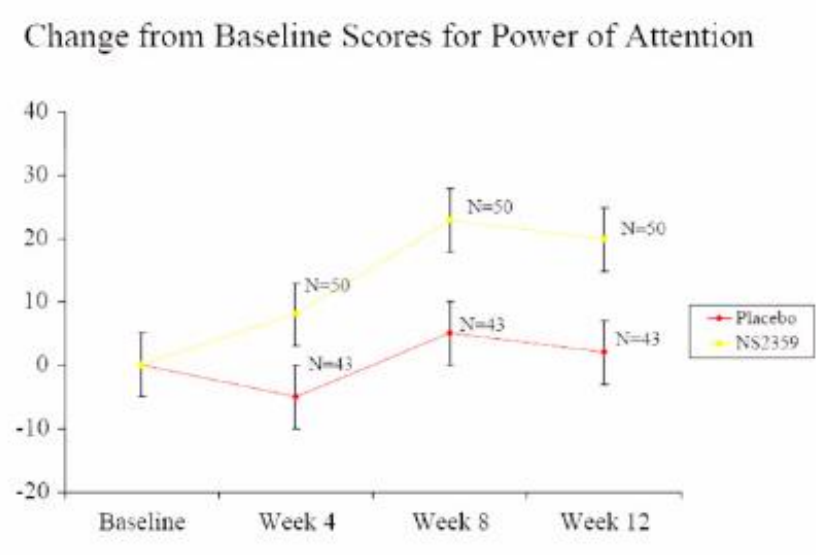
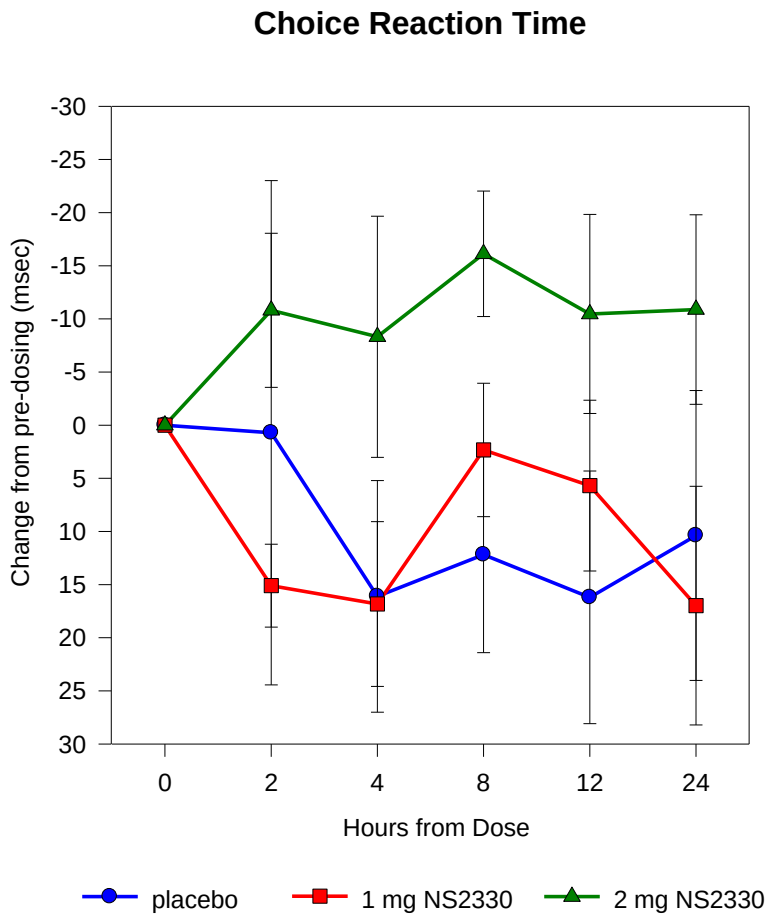


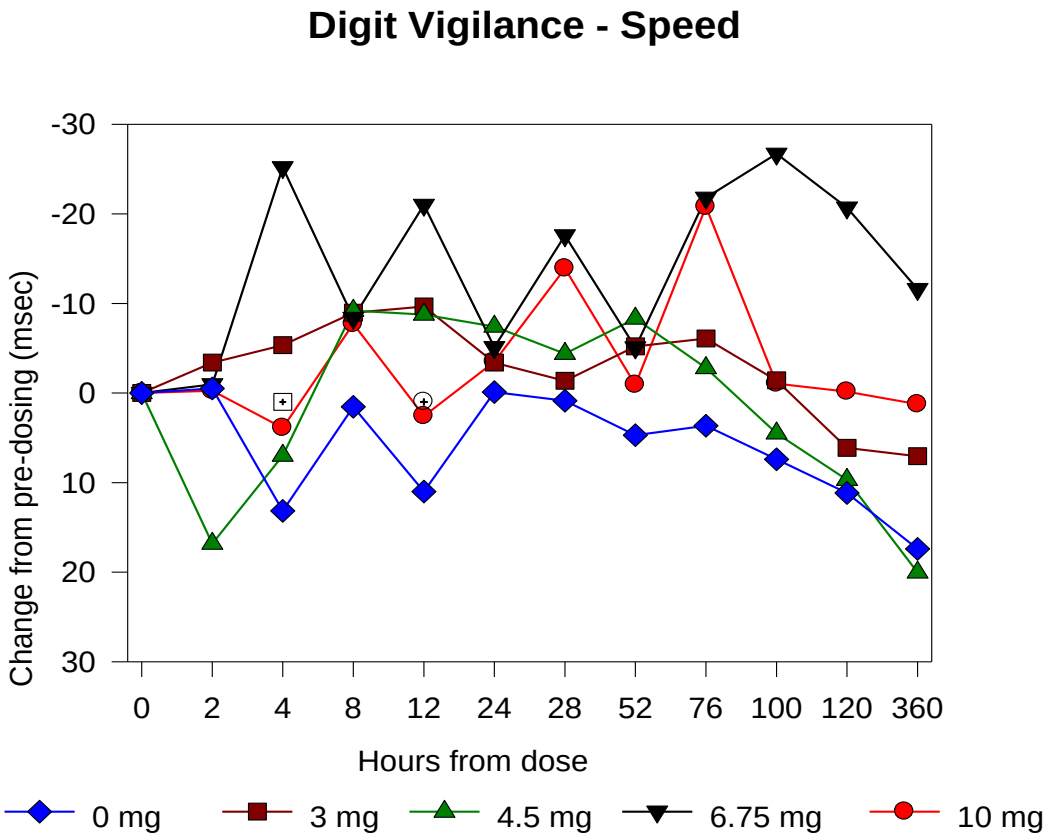
Figure 4
Change from baseline scores for Power of Attention over the study period (Mean +/- SEM). Improvements from baseline are plotted to ascend.

NS2330 Improved attention with high dose n=16 first to man



Jones S, Jensen NO, Oliver S, Wesnes KA (1999)
First in man cognitive effects of NS2330, a novel monoamine reuptake inhibitor, in volunteers. Journal of Psychopharmacology 13: A26

Improvements to attention over placebo (blue line) n=24 SAD Study



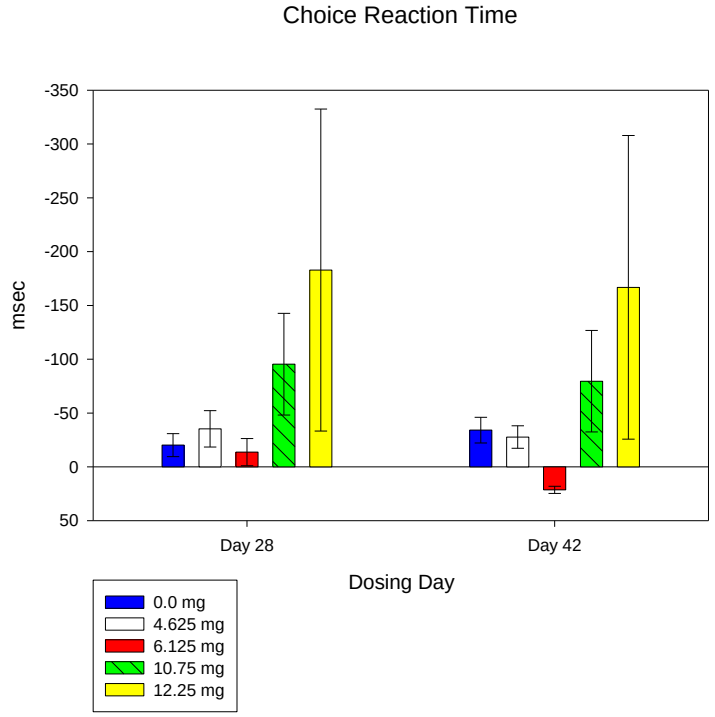
Wills K, Jensen NO, Oliver S, Wesnes KA (1999)
Cognitive effects of NS2330, a novel monoamine reuptake inhibitor, in volunteers.
Journal of Psychopharmacology 13: A27.

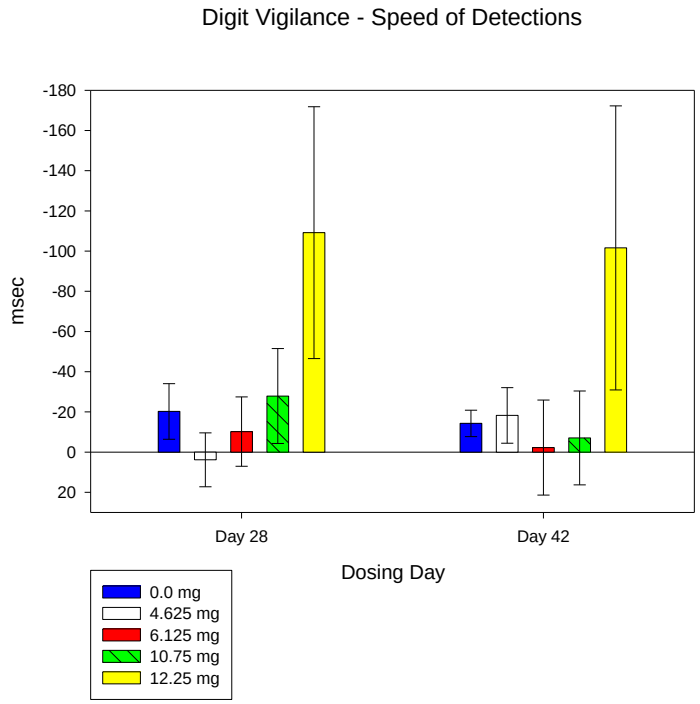
Study in Alzheimer's disease

- 32 Healthy male and female volunteers, aged 69 to 77, with mild memory impairment consistent with possible Alzheimer's disease (NINCDS-ADRDA guidelines; MMSE 20-26 inclusive).
- Placebo plus four active dose groups tested over 28 days
- CDR testing conducted Pre-Dose, at 28 days & 14 days later

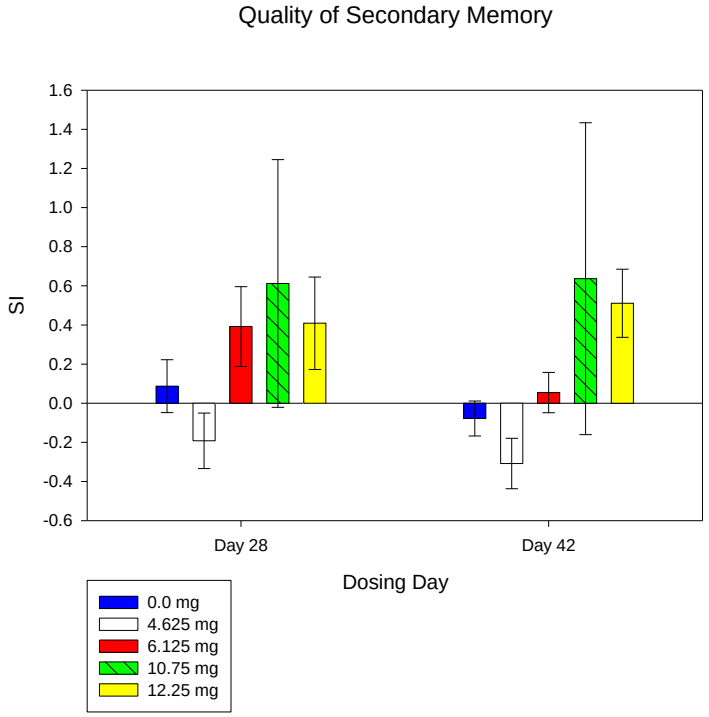
Keith A. Wesnes, Sheldon H. Preskorn, Sara Friesen, Chris Edgar, Birgit Ohrt Mikkelsen. NS 2330 enhances cognitive function in both normal volunteers and elderly volunteers with possible Alzheimer's disease ACNP, Hawaii, December 2001

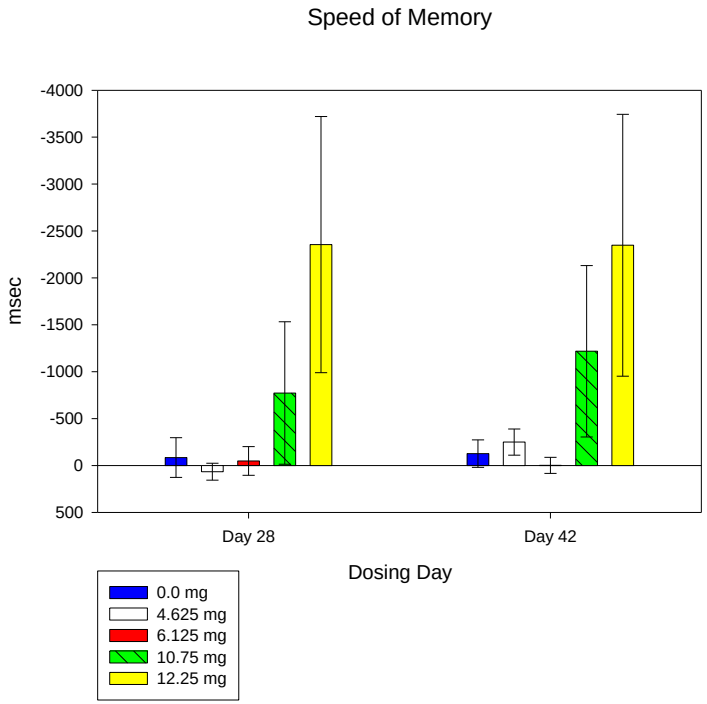
Dose dependent improvements to attention



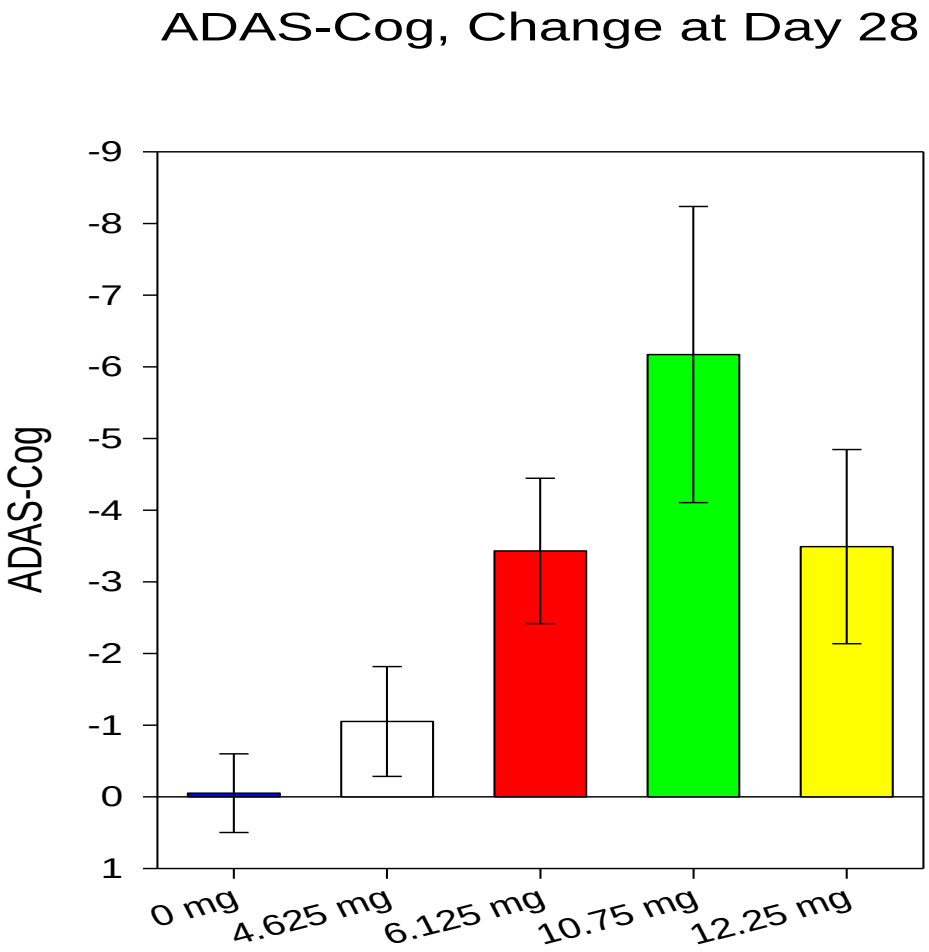


Dose dependent improvements to memory





Improvements on Day 28 to ADAS-Cog



Routine Phase I Studies in which Cognition Enhancement Identified (*Non-nicotinics*)

Intervention	Vols	n	Design	ATT & IP	WM & EF	EM/ LTM	Ref #
D-Cycloserine 5 & 15 mg	Elderly	24	x-over single dose	↔	↔	↑	173
E-5842 10 & 20 mg *sigma1 ligand*	Young	25	// group 7 days	↑	↑	↑	169
Flesinoxan *5HT1A full agonist*	Elderly	36	x-over 11 days	↑	↔	↔	117
HOE 427 *ACTH analogue*	Elderly	20	x-over	↑	↑	↔	95
Moclobemide *MAO-A inhibitor*	Young	24	x-over single dose	↓	↔	↑	142
Moclobemide *MAO-A inhibitor*	Elderly	27	x-over single dose	↔	↑	↑	140,141
Modafinil 200 mg	Young	36	// group single dose	↑	↑		129
NS2359 *5HT, NE & DA Reup. Inhibitor*	Young	40	single dose	↑	↔	↑	9
NS2330 *5HT, NE & DA Reup. Inhibitor*	Young	16	single dose	↑	↑	↔	41
NS2330 *5HT, NE & DA Reup. Inhibitor*	Young	32	single dose	↑	↑	↑	156
S17092 *prolyl endopeptidase Inhibitor*	Young	36	// group single dose	↑	↔	↑	65
S17092 *prolyl endopeptidase Inhibitor*	Elderly	36	// group single dose	↔	↑	↑	66
Sibutramine *5HT& NE Reup. Inhibitor*	Young	20	x-over single dose	↑	↔	↑	124
SB-202026 *muscarinic agonist*	Elderly	20	x-over single dose	↑	↔	↔	159
Tenilsetam 150 & 300 mg	Young	18	x-over single dose	↑	↑	↑	143

↑= statistically significant enhancement ↔ = no significant change ↓= significant impairment

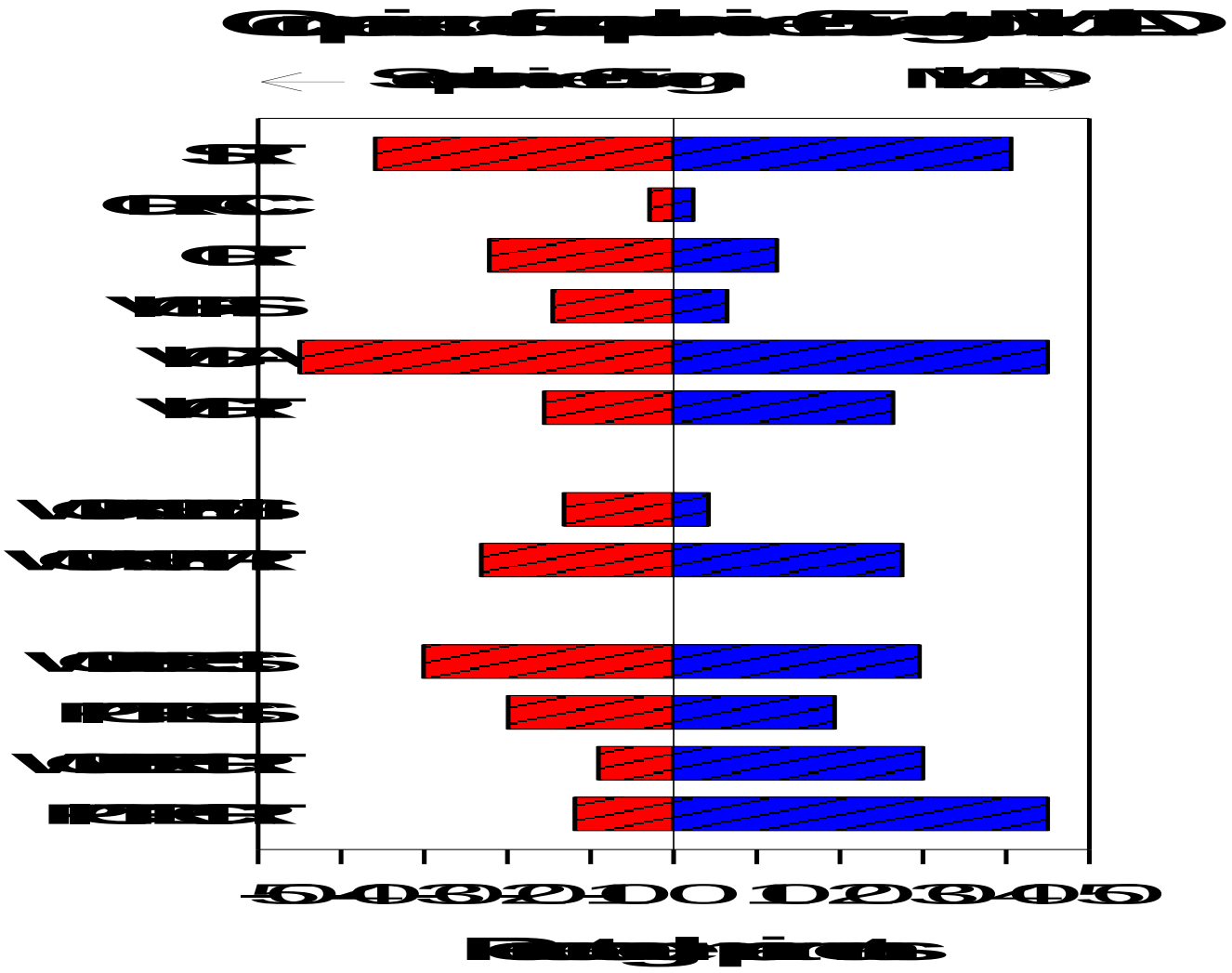
Empty box = domain not assessed ATT & IP = Attention & Information Processing

WM & EF = Working Memory &/or Executive Function

EM / LTM = Episodic Memory / Long-Term Memory

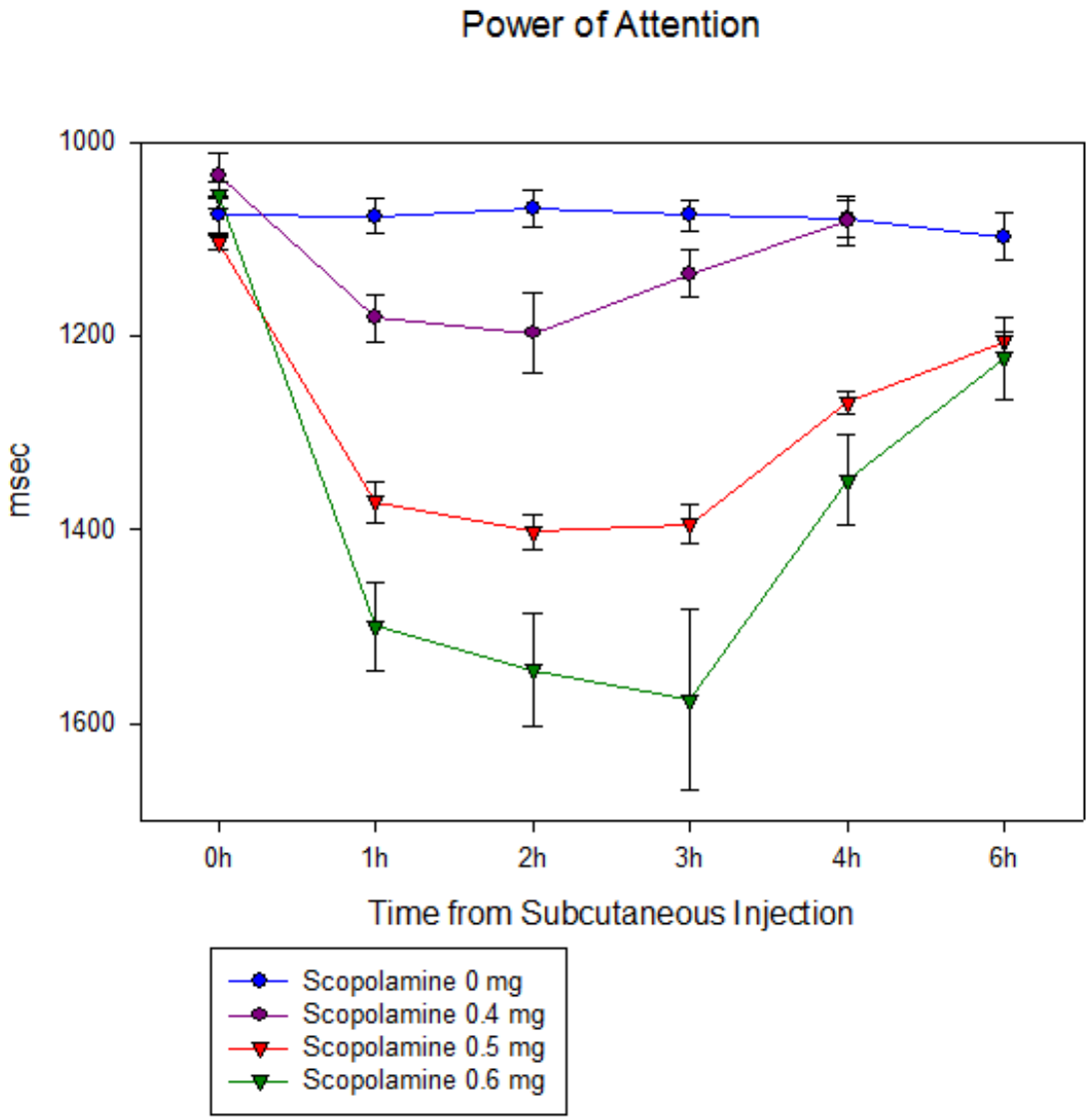
Scopolamine Model

In volunteers scopolamine mimics the profile of cognitive deficits identified using the same tests in Alzheimer's patients

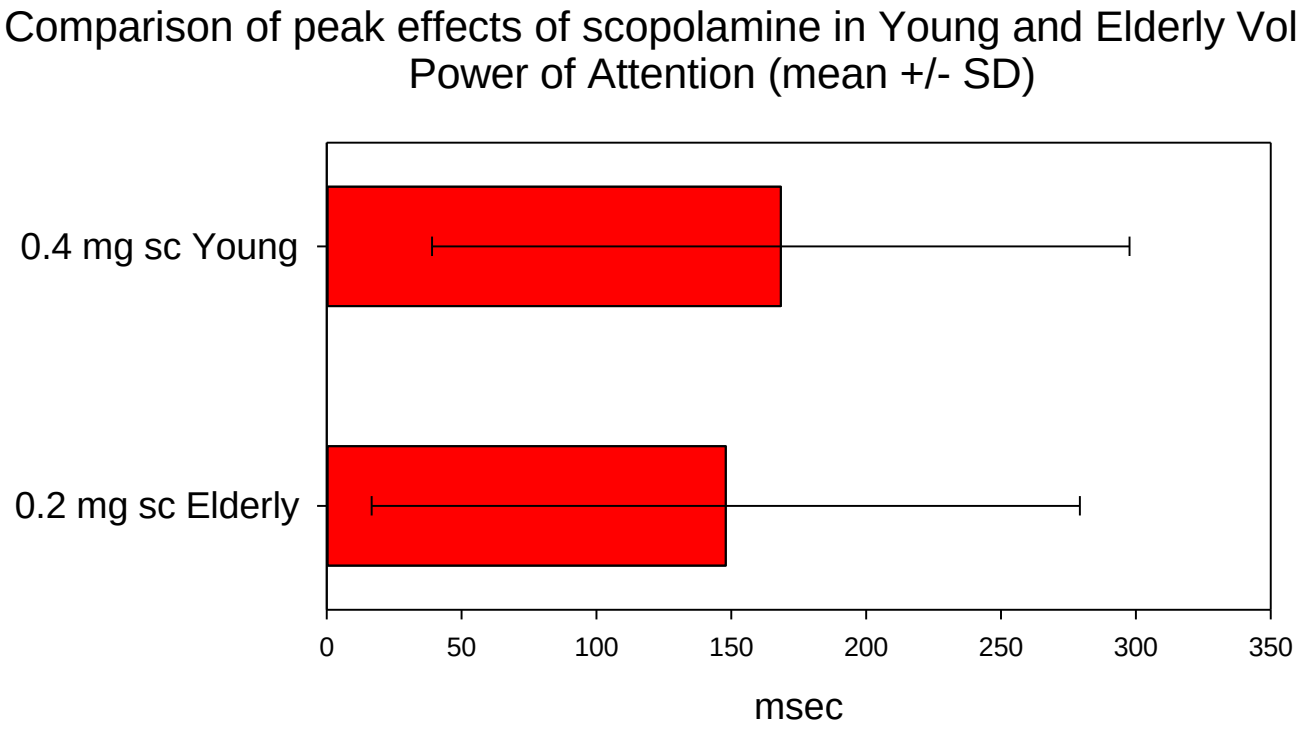


Optimum time & dose profile in young volunteers

0.5 mg sc provides the best balance of effect duration and acceptability of side-effects



Effects of ageing on scopolamine deficits
The elderly are more sensitive to scopolamine



Physostigmine

Reprinted from **Aging and Alzheimer's Disease**
Volume 640 of the *Annals of the New York Academy of Sciences*
December 3, 1991

Cholinesterase Inhibition in the Scopolamine Model of Dementia

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GABRIELA JERTZ,[b] MICHAEL MURPHY,[c] AND
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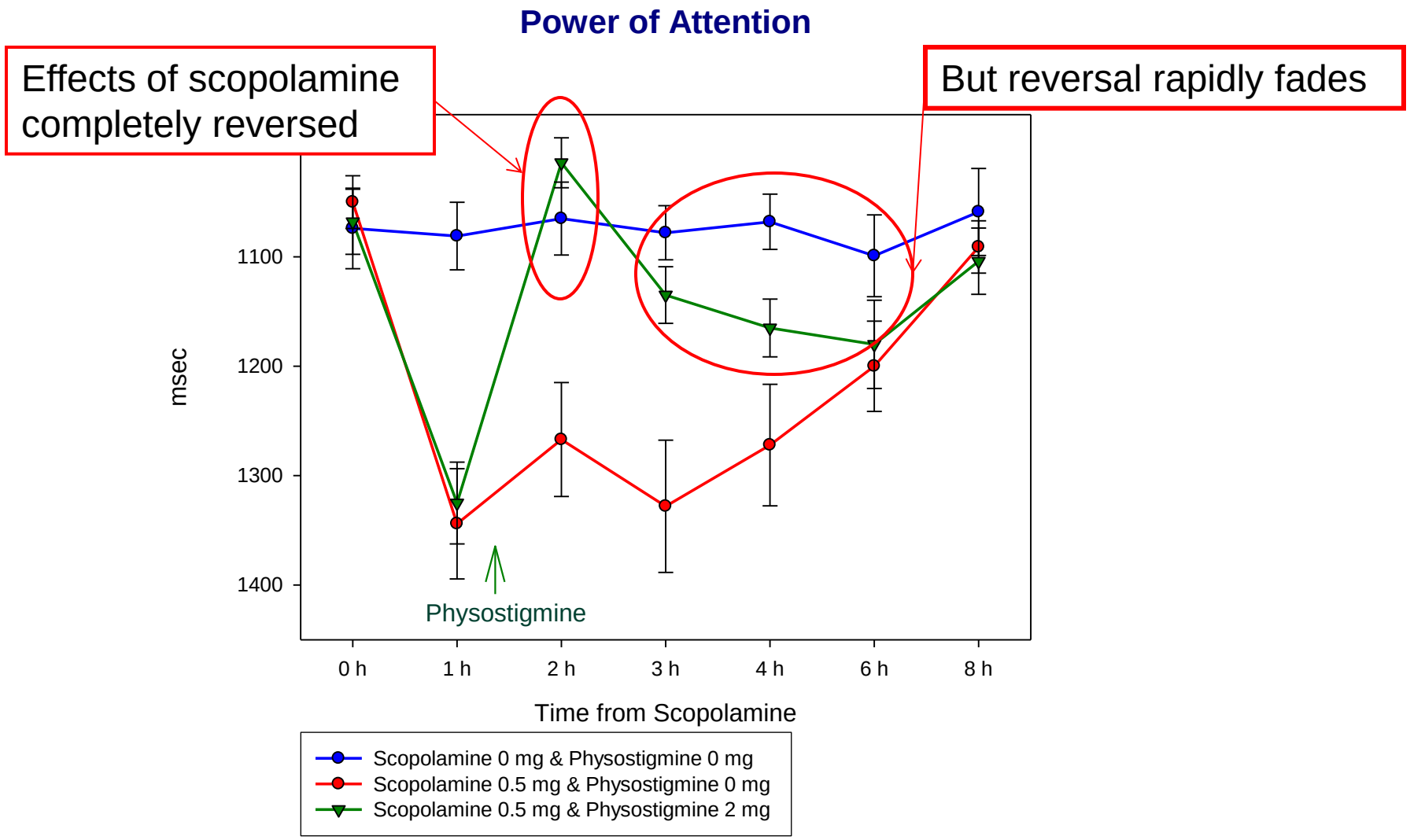
Physostigmine reversed effects of scopolamine on all CDR System measures

TABLE 2. Ability of Physostigmine (2.0 mg sc) to Antagonize Impairments Produced by Scopolamine (0.5 mg sc) on Cognitive Efficiency[a]

Measure	Scopolamine (mg): 0.5 Physostigmine (mg): 0	0.5 2.0	$p <$
Vigilance—accuracy	−15%	4%	0.01
Vigilance—speed	−16%	5%	0.01
Simple reaction time	−31%	5%	0.01
Choice reaction time	−17%	3%	0.05
Information processing—accuracy	−9%	5%	0.01
Information processing—speed	−11%	0%	0.05
Memory scanning			
Sensitivity	−15%	−2%	0.01
Speed	−31%	4%	0.01
Immediate recall—accuracy	−27%	−9%	0.01
Delayed recall—accuracy	−27%	0%	0.01
Word recognition			
Sensitivity	−5%	12%	0.01
Speed	−4%	4%	0.01
Subjective alertness	−31%	−4%	0.01

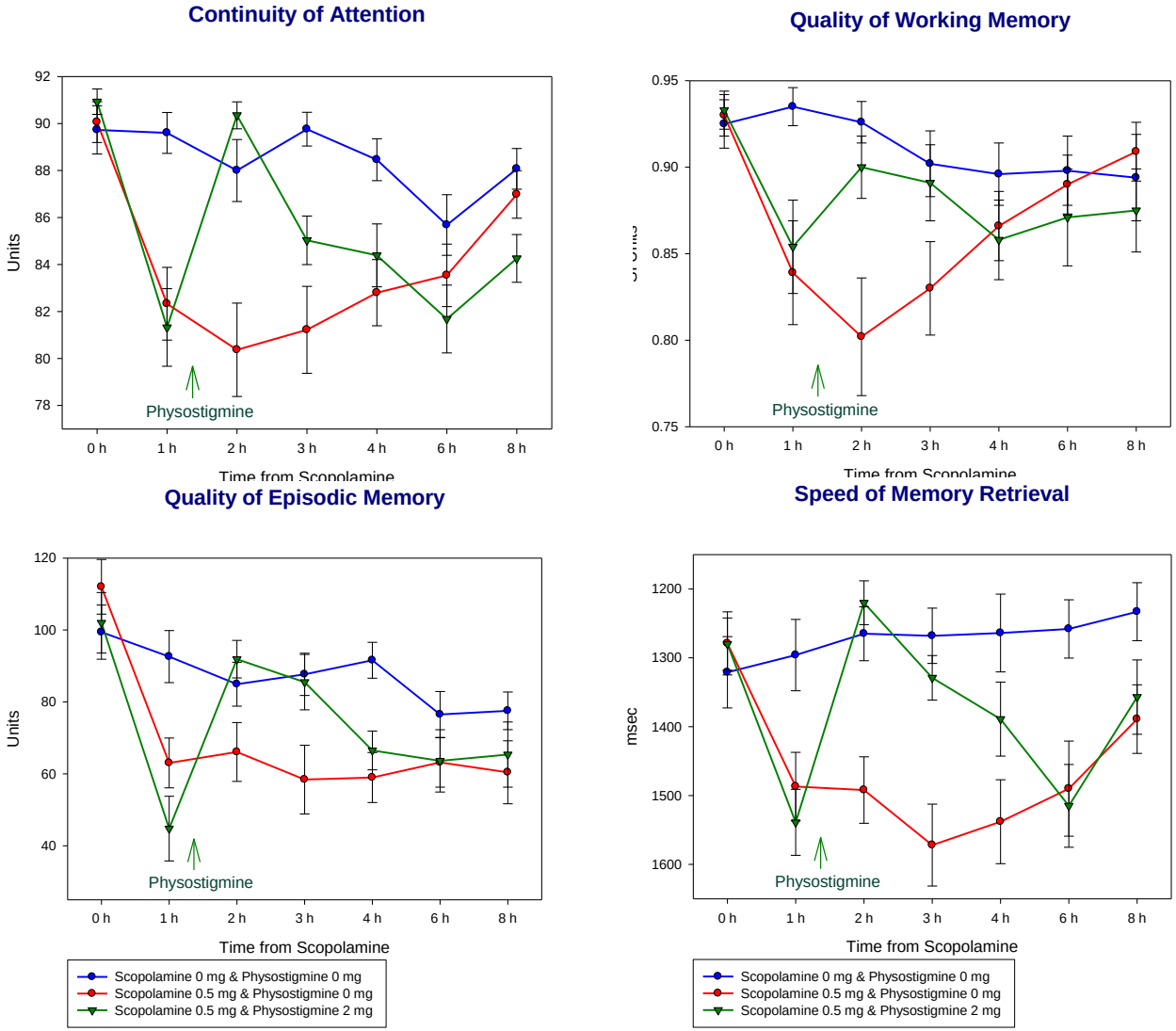
[a] Scores represent the percentage differences to a placebo-scopolamine condition, the negative signs indicating impaired efficiency. Significance levels refer to the ability of physostigmine to antagonize the effects of scopolamine.

Ability of physostigmine to temporarily reverse the effects of scopolamine on attention



Data from: Wesnes KA, Simpson PM, White L, Pinker S, Jertz G, Murphy M, Siegfried K (1991). Cholinesterase inhibition in the scopolamine model of dementia. Annals of the New York Academy of Sciences 640: 268-271.

Pattern consistent over all cognitive domains



Data from: Wesnes KA, Simpson PM, White L, Pinker S, Jertz G, Murphy M, Siegfried K (1991). Cholinesterase inhibition in the scopolamine model of dementia. Annals of the New York Academy of Sciences 640: 268-271.

Velnacrine, an analogue of THA

- Velnacrine, an anticholinesterase is found to be effective in the scopolamine model using the CDR system
- A Phase IIA 34 Alzheimer's patient, 10 day randomised, placebo controlled, cross-over study, double-blind, proof of concept trial was conducted in 4 countries (UK, Germany, France & Belgium)
- The same CDR measures were improved in patients as in volunteers in the model, showing the predictability of the scopolamine model, and also illustrating the sensitivity of the CDR System.

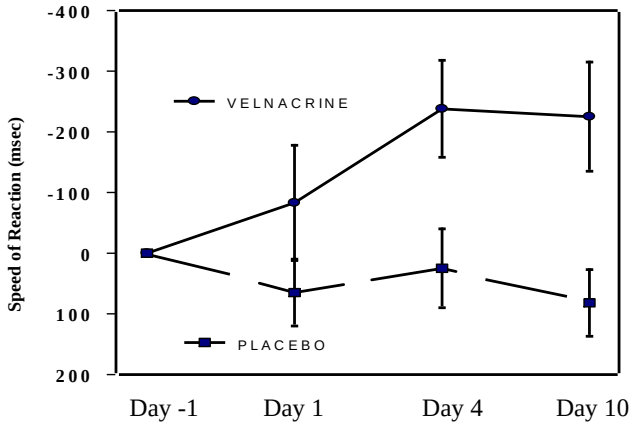
Siegfried KR (1993). Pharmacodynamic and early clinical studies with velnacrine. Acta Neurol Scand 149: 26-28

Goa KL, Fitton A. (1994). Velnacrine in Alzheimer's Disease: An Initial Appraisal of its Clinical Potential. CNS Drugs 1: 232-240.

Effects of velnacrine in AD (n=34)

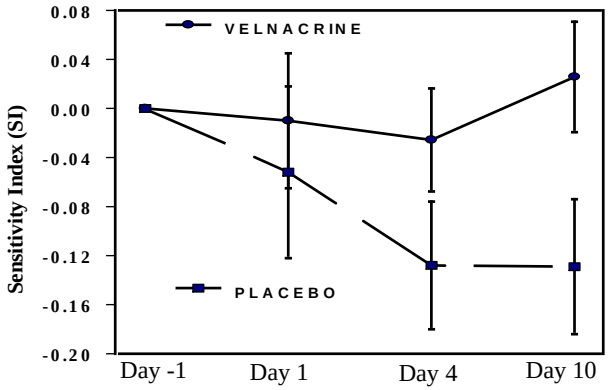
ABILITY TO FOCUS ATTENTION AND MAKE DECISIONS

Choice Reaction Time



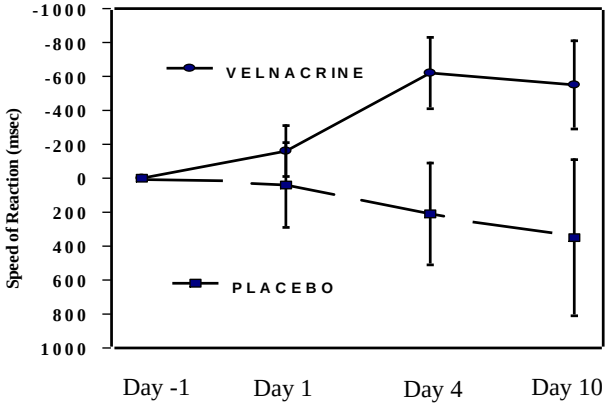
ABILITY TO CORRECTLY RECOGNISE WORDS

Word Recognition Sensitivity



TIME TAKEN TO CORRECTLY RECOGNISE WORDS

Word Recognition Speed



Effects replicated in 735 Alzheimer's patients in a double-blind, placebo controlled, 6-week, dose-ranging study using the ADAS-cog.

J Neural Transm (1996) 103: 1105–1116

Journal of Neural Transmission

© Springer-Verlag 1996
Printed in Austria

Velnacrine for the treatment of Alzheimer's disease: a double-blind, placebo-controlled trial

F. P. Zemlan and **The Mentane Study Group***

Alzheimer's Research Center, Department of Psychiatry, University of Cincinnati, College of Medicine, Cincinnati, OH, U.S.A.

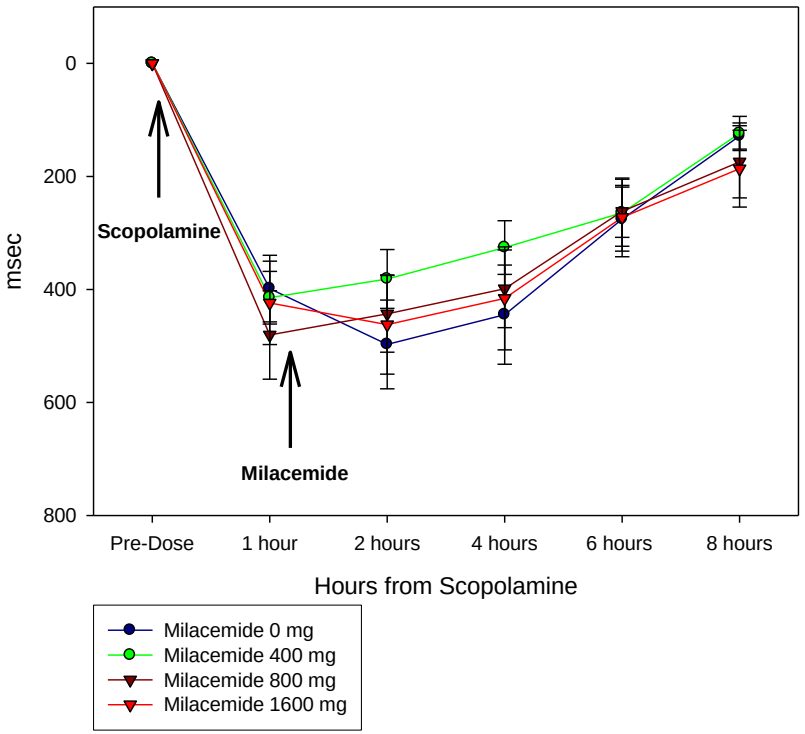
Accepted May 6, 1996

SUMMARY

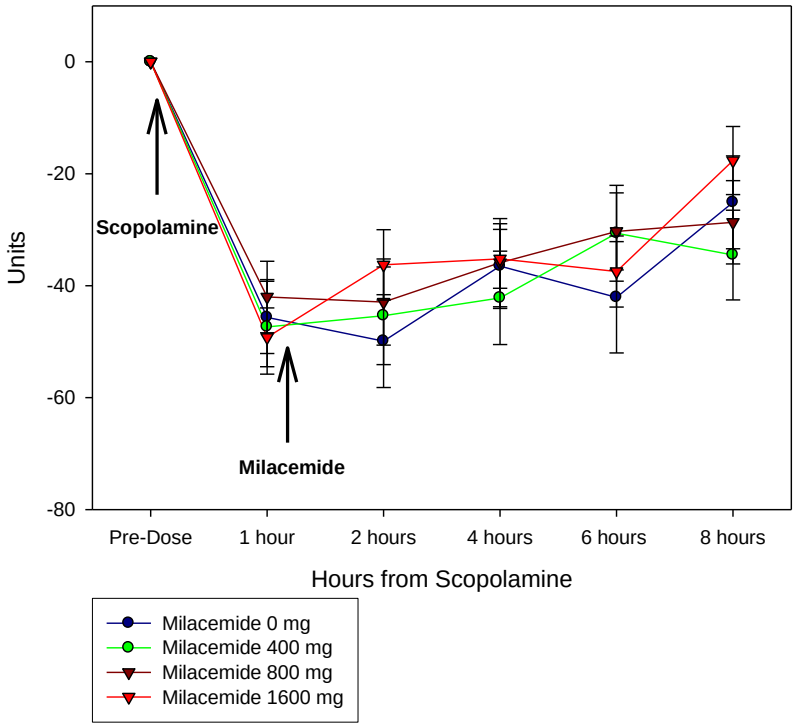
- Patients treated with velnacrine scored better on the cognitive subscale of the ADAS than placebo patients ($P < 0.001$)
- Clinical Global Impression of Change scores of velnacrine-treated patients were significantly improved at the end of the 6 weeks of treatment when compared to those of placebo patients ($P < 0.05$).

Milacemide, a glycine pro-drug is ineffective in the Scopolamine model

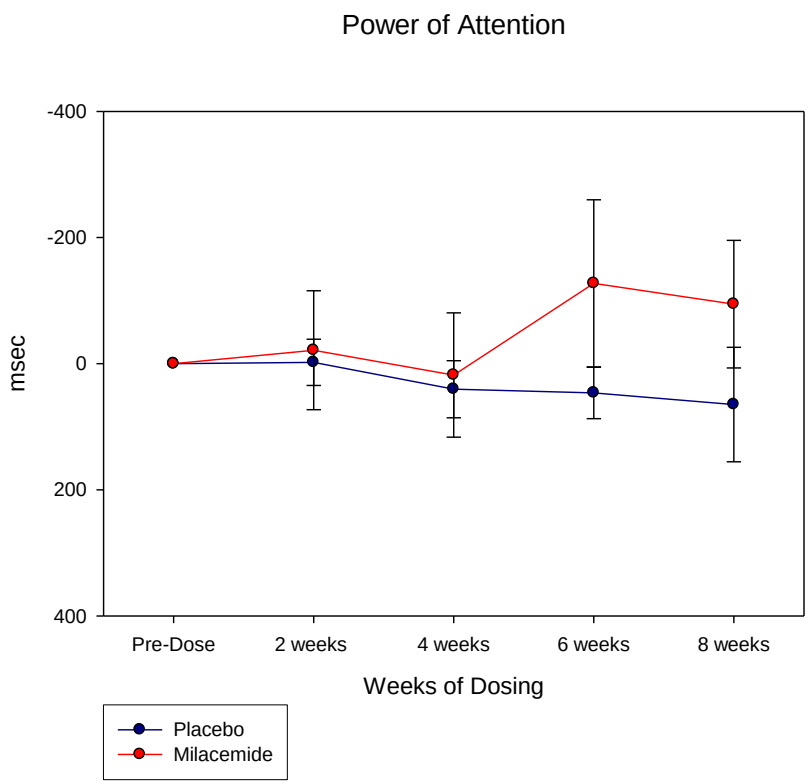
Power of Attention

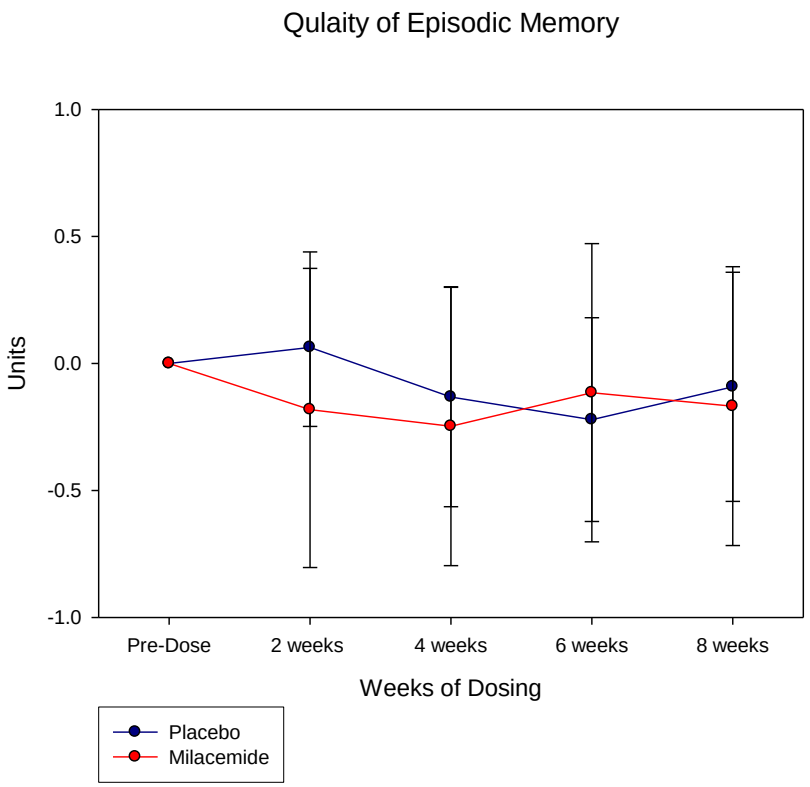


Quality of Episodic Memory



Milacemide is also ineffective on the same CDR System tests when administered to Alzheimer's patients, and in other trials with a range of scales





Herting RL (1991). Milacemide and other drugs active at glutamate NMDA receptors as potential treatment for dementia. Annals of the New York Academy of Sciences 640: 237-240.

Use of the CDR System in the Scopolamine Model to Predict Cognition Enhancement Potential in Phases II & III

	Scopolamine Model	Phase II & III Trials
Nicotine	✓	✓Elderly ✓ MCI ✓AD
ABT-089	✓	✓ADHD ✖ AD
Piracetam	✓	✓Elderly ✓ADHD ✓AD
Aniracetam	✓	✓Elderly ✓ AD
Milacemide	✖	✖AD
D-Cycloserine	✓	✓Short *not* long term dosing AD ✓Schizophrenia
Moclobemide	✓	✓ MDD
Physostigmine	✓	✓AD
Huperzine	✓	✓AD
Aricept	✓	✓AD
Velnacrine	✓	✓AD
FK960	✓	Not yet tested

Sleep Deprivation Models

Neuropsychobiology
Editors: J. Mendlewicz, Brussels; Ch. Pull, Luxembourg; W. Janke, Würzburg; H. Künkel, Hannover

Reprint
Publisher: S. Karger AG, Basel
Printed in Switzerland

Neuropsychobiology *15:* 187–191 (1986)

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0302–282X/86/0154–0187$2.75/0

Effects of Temazepam on Sleep Quality and Subsequent Mental Efficiency under Normal Sleeping Conditions and following Delayed Sleep Onset

K. Wesnes, D.M. Warburton

Department of Psychology University of Reading, UK

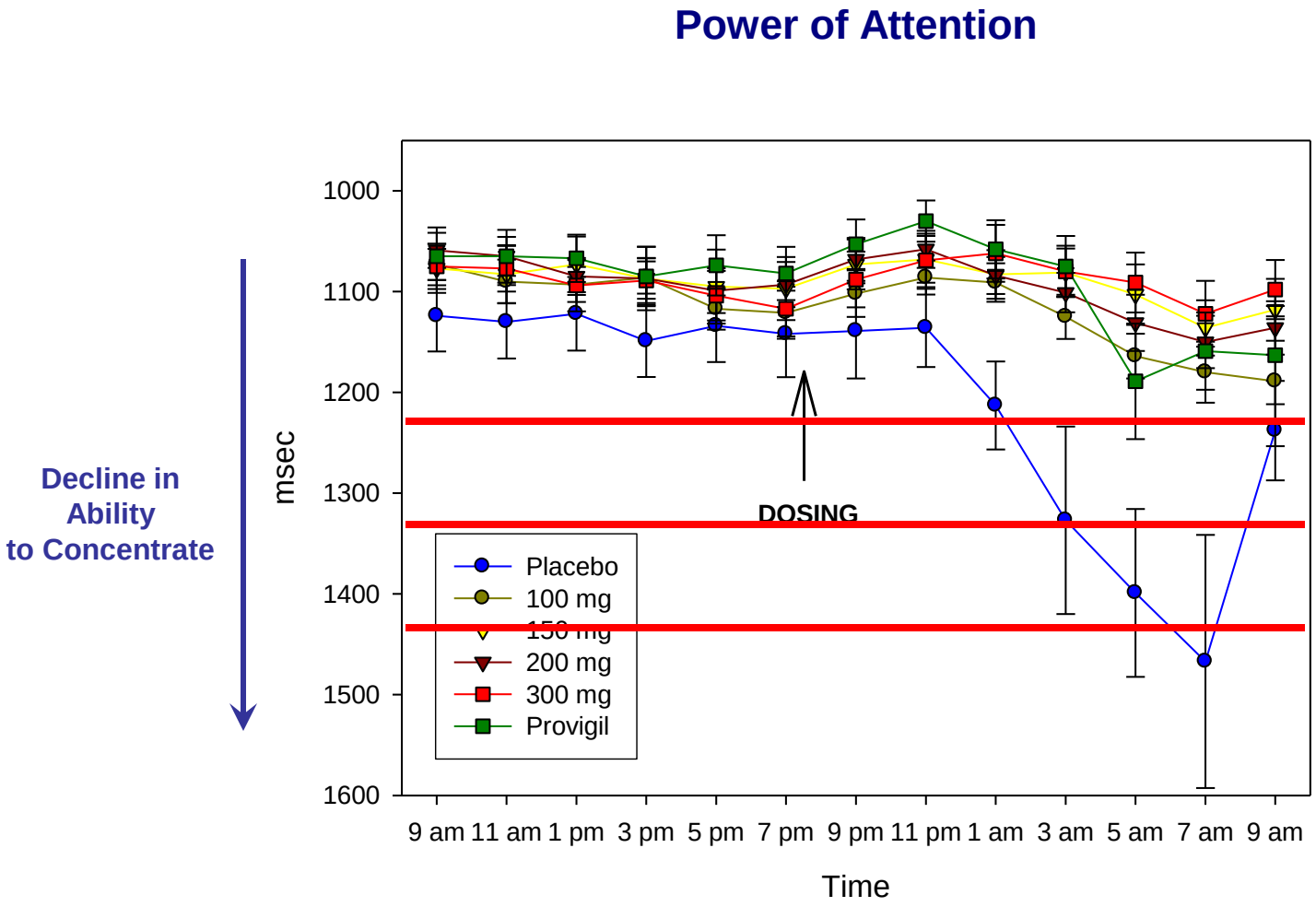
- 24 healthy volunteers
- Randomised, double blind, placebo controlled 2 way crossover design
- Subjects kept awake until evenings before & tested in Laboratory 10 h later next morning

Table III. Responses to St. Mary's Hospital sleep questionnaire together with the significance levels of the between condition comparisons in experiment 2

	Placebo	Temazepam 20 mg	p
Time fell asleep	7 h 35 min	7 h 29 min	
Time finally woke up	13 h 08 min	13 h 59 min	0.031
Time got up	13 h 33 min	14 h 20 min	0.016
Difficulty getting to sleep	1.39	1.00	0.029
Depth of sleep	5.04	6.00	0.054
Quality of sleep	3.87	4.82	0.012
Satisfaction with sleep	3.13	4.04	0.003
Hours asleep	5.47	6.42	0.022
Number of times woke up	2.95	1.83	0.02
Clearheadedness on waking	2.87	2.96	

Armodafinil & Modafinil shown to prevent cognitive deterioration in sleep deprivation model

108 healthy young volunteers tested over 24 hours without sleep



Wesnes KA, Macher J-P (2004) Modafinil reverses the marked attentional deficits produced by acute sleep deprivation in healthy volunteers. Journal of Psychopharmacology 18 (Suppl): A48

Respiratory Medicine (2007) **101**, 616–627

ELSEVIER

respiratoryMEDICINE

Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome

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ORIGINAL ARTICLE

The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy*

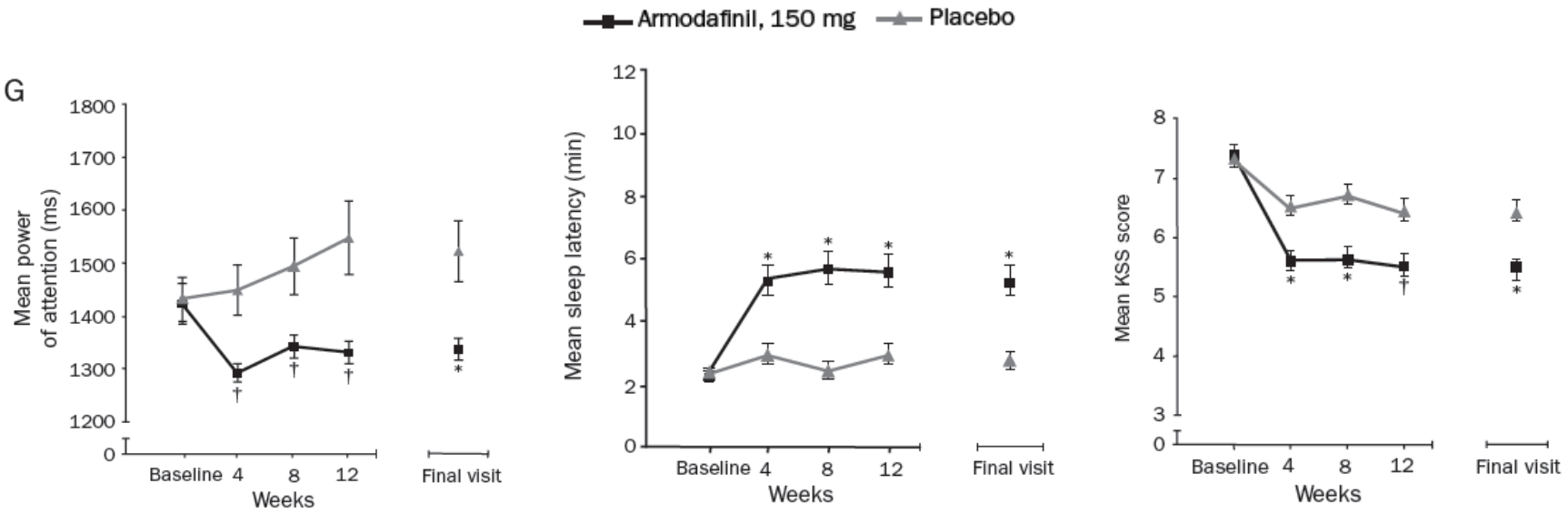
John R. Harsh[a], Roza Hayduk[b], Russell Rosenberg[c], Keith A. Wesnes[d], James K. Walsh[e], Sanjay Arora[f], Gwendolyn E. Niebler[f] and Thomas Roth[g]

ORIGINAL ARTICLE

Mayo Clin Proc. 2009;84(11):958-972

Armodafinil for Treatment of Excessive Sleepiness Associated With Shift Work Disorder: A Randomized Controlled Study

CHARLES A. CZEISLER, PHD, MD; JAMES K. WALSH, PHD; KEITH A. WESNES, PHD; SANJAY ARORA, PHD†; AND THOMAS ROTH, PHD



Not only do Phase I data predict response in patients, but CDR System attention tests, Sleep Latency and Karolinska Sleepiness Scale all show same pattern of response.

Case Study: Effects of modafinil in breast cancer survivors

The Effect of Modafinil on Cognitive Function in Breast Cancer Survivors

Sadhna Kohli, PhD, MPH[1]; Susan G. Fisher, PhD[2]; Yolande Tra, PhD[3]; M. Jacob Adams, MD, MPH[2]; Mark E. Mapstone, PhD[4]; Keith A. Wesnes, PhD[5]; Joseph A. Roscoe, PhD[6], and Gary R. Morrow, PhD, MS[6]

BACKGROUND: The authors conducted a randomized clinical trial examining the effects of modafinil in reducing persistent fatigue in patients after treatment for cancer and performed secondary analyses to assess the effect of modafinil on cognitive function. **METHODS:** Breast cancer patients who reported a score of ≥2 on the Brief Fatigue Inventory were enrolled in the study. In phase 1 (P1), patients received 200 mg modafinil open-label once daily for 4 weeks. In phase 2 (P2), patients with a positive response after P1 were randomized either to an additional 4 weeks of modafinil or to placebo. Tests of memory and attention selected from the Cognitive Drug Research (CDR) computerized cognitive assessment were performed at baseline (before modafinil) and after completing phases 1 and 2. The paired differences for each test score were subjected to a Wilcoxon signed rank test. **RESULTS:** Of the 82 women who were enrolled, 76 completed P1, and 68 completed all assessments in the study. Modafinil had a significant effect on the Speed of Memory (P=.0073) and Quality of Episodic Memory (P < .0001) during P1 of the study. After randomization at Week 8, those patients who continued modafinil demonstrated significantly greater improvement in Speed of Memory (P=.029), Quality of Episodic Memory (P=.0151), and mean Continuity of Attention (P=.0101) relative to the group that was switched to placebo. **CONCLUSIONS:** The authors found that modafinil improved cognitive performance in breast cancer survivors by enhancing some memory and attention skills. Although confirmation is needed, these findings suggest that modafinil may enhance quality of life in this patient population. **Cancer 2009;115:2605–16. © 2009 American Cancer Society.**

KEY WORDS: modafinil, cognitive function, memory, attention, breast cancer.

Residual Effects of Hypnotics

Neuropsychobiology
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Neuropsychobiology *11:* 255–259 (1984)

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0302–282X/84/0114–0255$2.75/0

A Comparison of Temazepam and Flurazepam in Terms of Sleep Quality and Residual Changes in Performance

K. Wesnes, D.M. Warburton

Department of Psychology, University of Reading, England

- 24 healthy volunteers
- Randomised, double blind, placebo controlled crossover design
- Subjects dosed at 10.30-11.30 evenings before & tested in Laboratory 10 h later next morning

Sleep Quality & Clearheadedness on Waking

Table I. Results of St. Marys Hospital Sleep Questionnaire

Question	Placebo-flurazepam	Flurazepam 30 mg	Placebo-temazepam	Temazepam 40 mg
Depth of sleep	4.8	6.2***	4	5.8***
Quality of sleep	4	5.2***	3.8	4.9***
Satisfaction with sleep	3.6	4.1**	3.5	4*
Asleep, h	7.6	8.1***	7.4	8.0***
Number of times woke up	2.4	1.3***	2.6	1.7
Clearheadedness on waking	3.6	2.7***	3.7	3.2
Difficulty getting to sleep				
Males	1.4	1.3	1.5	1.2
Females	1.8	1.1**	1.9	1.1**

Significance of differences between each drug and its placebo is shown; see text for details of statistical procedures. * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

RVIP - Impairments to accuracy & speed following Flurazepam both p<0.01
DSST & CFF - No significant changes

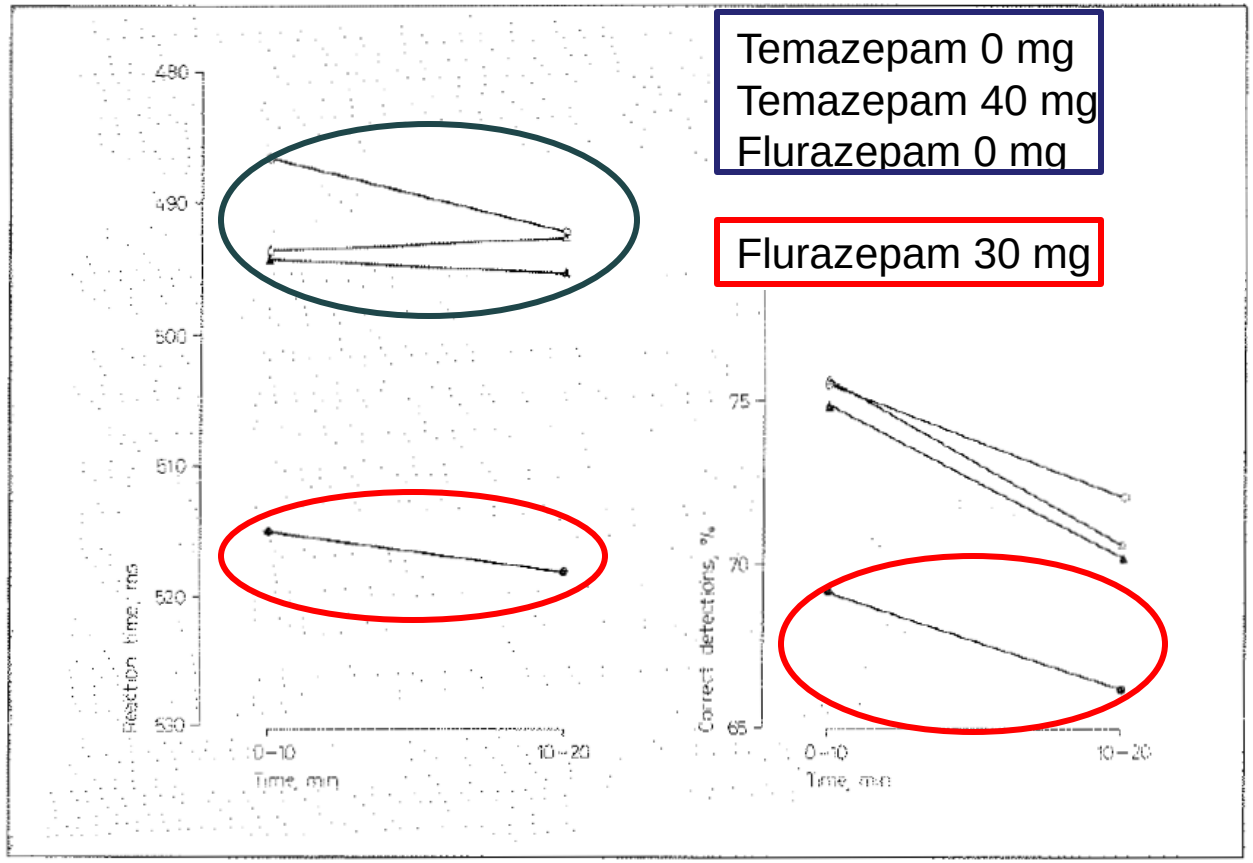
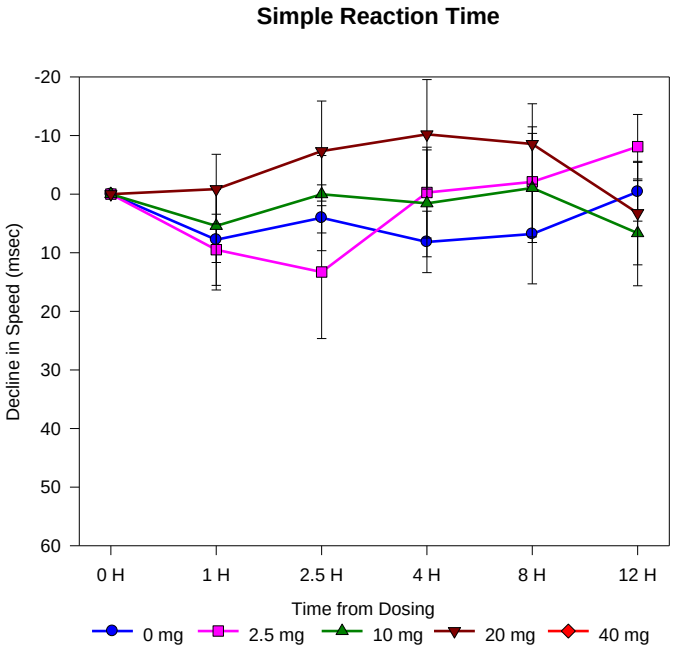


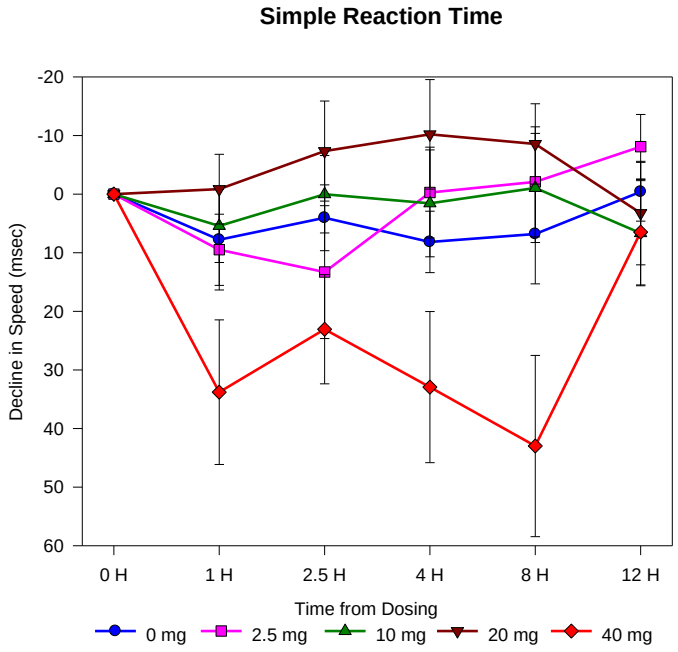
Fig. 1. The percentage of hits and the mean reaction times during each of the 2 successive stages of testing in the rapid visual information processing task.

Safety: Absence or relative absence of cognitive toxicity

Phase I study of M3 antagonist

- Compound designed to be free of central effects
- This was established up to 20 mg





McEwen J, Wesnes K, Rapeport WG, Williams S. (1995). The cognitive effects of single and multiple doses of UK 76,654, a selective M3 muscarinic antagonist, in healthy volunteers.
European Journal of Clinical Investigation 25, Suppl. 2: A64

Follow up compound – Darifenacin

Pharmacodynamic effects of darifenacin, a muscarinic M_3 selective receptor antagonist for the treatment of overactive bladder, in healthy volunteers

GARY G. KAY and KEITH A. WESNES†
Washington Neuropsychological Institute, Washington DC, USA and †Cognitive Drug Research Ltd, Goring-on-Thames, UK

Accepted for publication 10 June 2005

© 2005 BJU INTERNATIONAL | 96, 1055–1062 | doi:10.1111/j.1464-410X.2005.05745.x

OBJECTIVE

To evaluate the pharmacodynamic effects of darifenacin (a muscarinic M_3 selective receptor antagonist) and dicyclomine (an M_1 selective receptor antagonist) in healthy male volunteers.

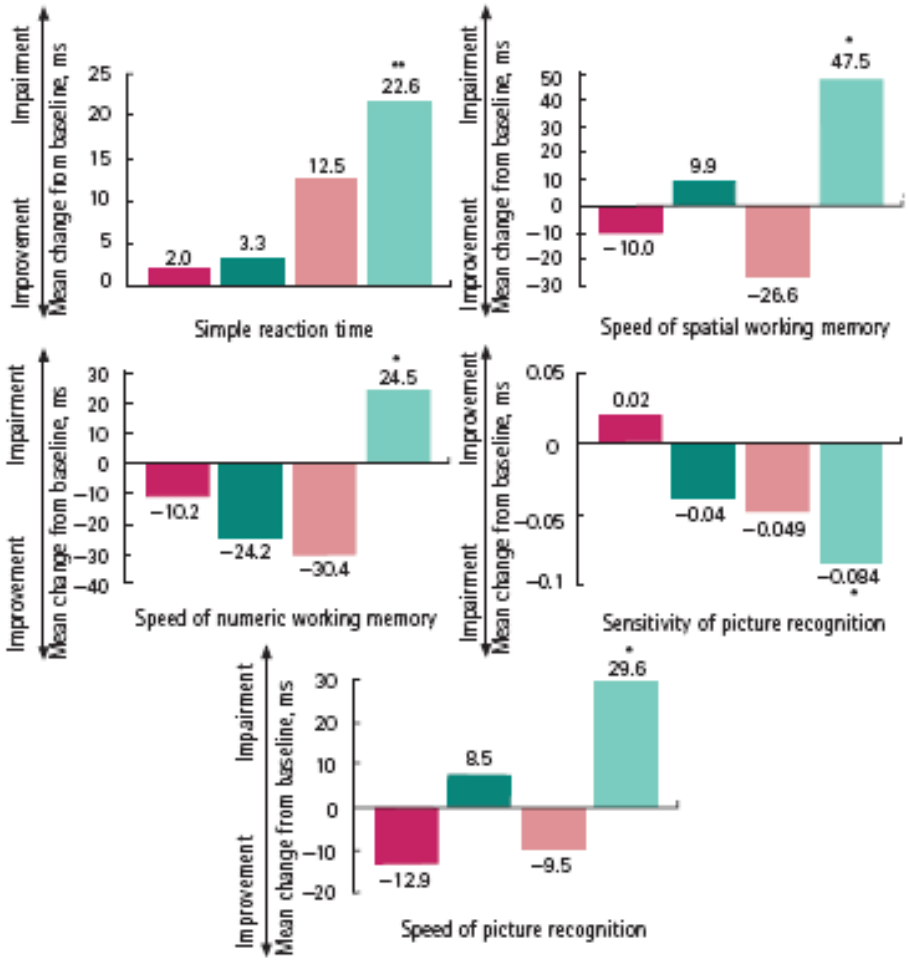
SUBJECTS AND METHODS

In this double-blind, four-way crossover study, 27 healthy men (aged 19–44 years) were randomized to receive darifenacin 7.5 mg or 15 mg once daily, dicyclomine 20 mg four times daily or matching placebo Each 7-day treatment period was separated by a 7-day washout. Multiple assessments of cognitive function, quantitative

CONCLUSIONS

Darifenacin did not affect cognitive, cardiac or visual function in healthy volunteers, a profile that may reflect its relative M_3 receptor selectivity and M_1/M_2 sparing properties.

*FIG. 1. Cognitive function in healthy men on the seventh day of treatment with darifenacin 7.5 mg and 15 mg once daily (green and light red bars respectively), dicyclomine 20 mg once daily (light green bars), and placebo (red bars). Mean change from baseline (before dose on the first day) at 2 h after the dose on the seventh day. *P < 0.05; **P < 0.01 relative to placebo.*



Findings of no effects with darifenacin in Phase I study of young volunteers replicated in large study in elderly volunteers.

0022-5347/05/1732-0493/0
THE JOURNAL OF UROLOGY®
Vol. 173, 493–498, February 2005
Printed in U.S.A.
DOI: 10.1097/01.ju.0000148963.21096.5d
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ASSESSMENT OF COGNITIVE FUNCTION OF THE ELDERLY POPULATION: EFFECTS OF DARIFENACIN

RICHARD B. LIPTON,*† KEN KOLODNER AND KEITH WESNES‡

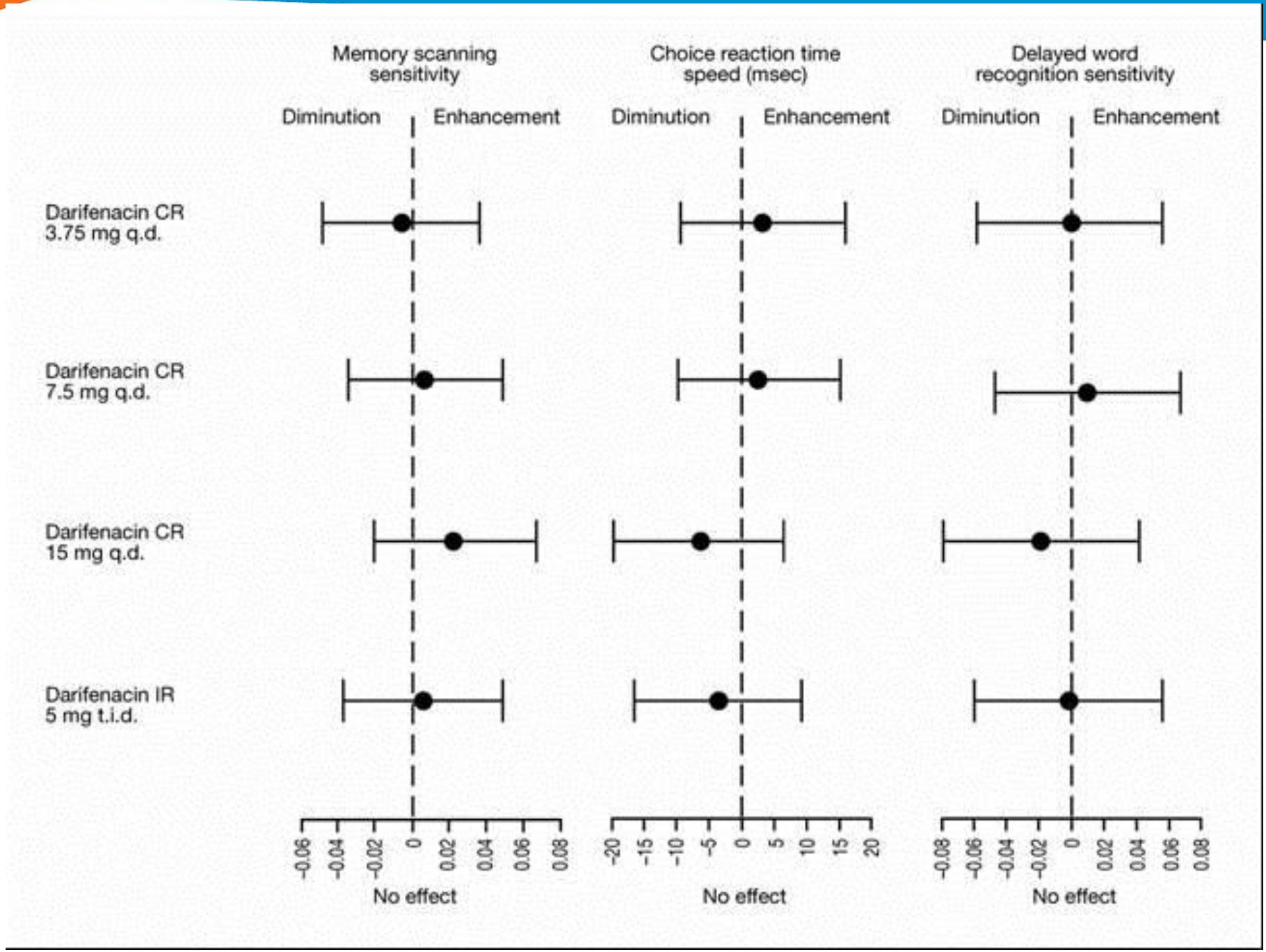
From the Departments of Neurology, Epidemiology and Population Health, Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine (RBL), Bronx, New York, Advance PCS (KK), Hunt Valley, Maryland, and Cognitive Drug Research, Ltd. (KW), Goring-on-Thames, United Kingdom

ABSTRACT

Purpose: Overactive bladder is common in the elderly population, which is susceptible to cognitive disorders and drug induced cognitive impairment. Existing overactive bladder treatments may cause adverse events, such as cognitive impairment, due to antagonism of the M_1 receptor in the central nervous system. In this study we evaluated the effect of darifenacin, an M_3 selective antagonist, on cognitive function in elderly volunteers without clinical dementia.

Materials and Methods: This double-blind, 3-period crossover study randomized 129 volunteers 65 years or older with no/mild cognitive impairment to receive 3 of 5 treatments, namely darifenacin controlled release (3.75, 7.5 or 15 mg once daily), darifenacin immediate-release (5 mg 3 times daily) or matching placebo for 14 days. Each treatment period was separated by 7 days of washout. Cognitive function tests were completed at baseline and at treatment end.

Conclusions: In elderly volunteers 2 weeks of treatment with darifenacin had no effect on cognitive function compared with baseline and it was not significantly different from placebo. This may be related to its M_3 receptor selectivity with negligible M_1 receptor antagonism.


Memory scanning sensitivity
Diminution
Enhancement
Choice reaction time speed (msec)
Diminution
Enhancement
Delayed word recognition sensitivity
Diminution
Enhancement
Darifenacin CR 3.75 mg q.d.
Darifenacin CR 7.5 mg q.d.
Darifenacin CR 15 mg q.d.
Darifenacin IR 5 mg t.i.d.
-0.06
-0.04
-0.02
0
0.02
0.04
0.06
0.08
No effect
-20
-15
-10
-5
0
5
10
15
20
No effect
-0.08
-0.06
-0.04
-0.02
0
0.02
0.04
0.06
0.08
No effect

Developed under the direction of Novartis Pharmaceuticals Corporation. Contains promotional material.

Enablex® (darifenacin) EXTENDED-RELEASE TABLETS
once daily 7.5mg or 15mg
Bladder effective and M_3 selective

PRESCRIBE ENABLEX FOR THE CONTROL OF YOUR OAB PATIENTS...

OAB control

No effect on cognitive function*[1]

Documented QT safety[2]
No increase in heart rate†[3]

In balance with ENABLEX

IN THE LITERATURE

Long-term treatment with darifenacin for overactive bladder: Results of a 2-year, open-label extension study
Haab et al. *BJU Int*, 2006.

QT and QTc interval with standard and supra-therapeutic doses of darifenacin, a muscarinic M_3 selective receptor antagonist for the treatment of overactive bladder

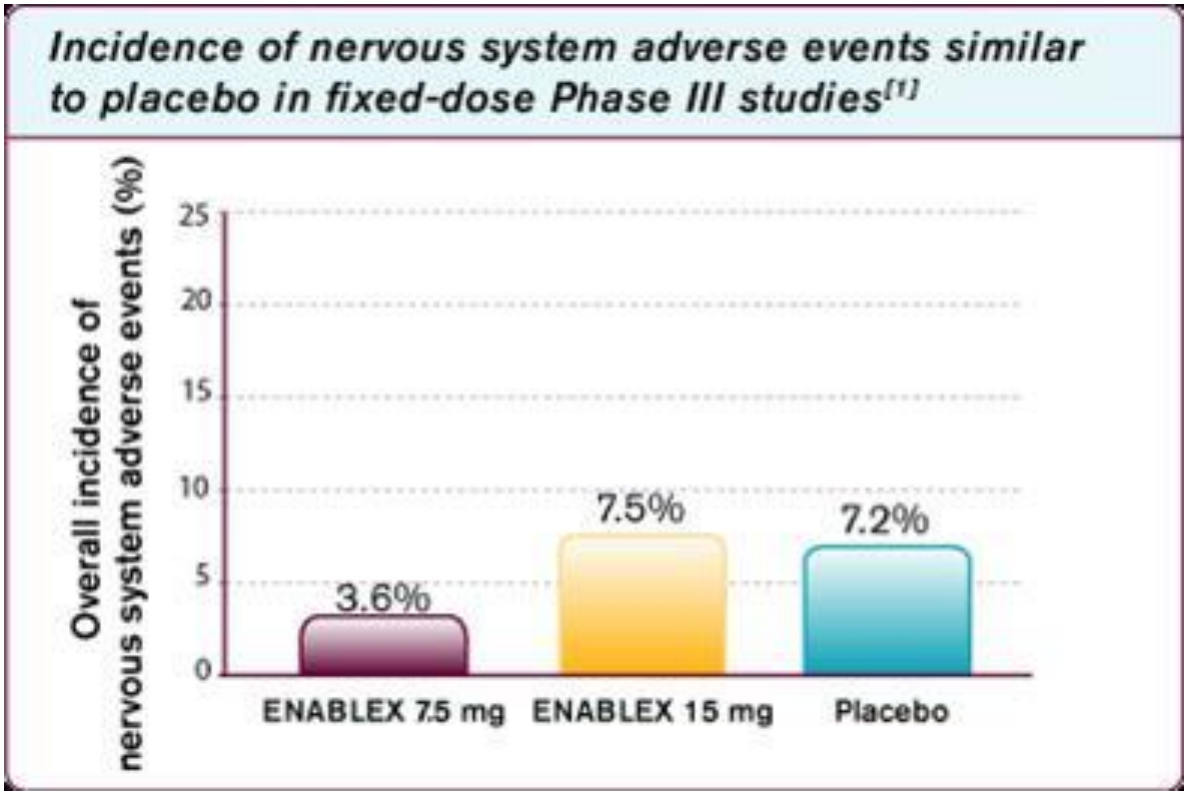
Data from Phase I thus predictive to patients

ENABLEX:

THERAPY THAT IS ON COURSE WITH LOW

INCIDENCE OF CNS AND CARDIAC EFFECTS

Enablex® (darifenacin) EXTENDED-RELEASE TABLETS once daily 7.5mg or 15mg



www.medscape.com/infosite/enablex

Another M3 specific compound found to be free of unwanted cognitive impairment, while oxybutynin impaired function in the elderly.

Original Research

Expert Opinion

1. Introduction
2. Patients and methods
3. Results
4. Discussion
5. Conclusions

Exploratory pilot study assessing the risk of cognitive impairment or sedation in the elderly following single doses of solifenacin 10 mg

Keith A Wesnes[†], Chris Edgar, Reiner N Tretter & John Bolodeoku
[†] *Cognitive Drug Research Ltd, CDR House, Gatehampton Road, Goring-on-Thames, RG8 0EN, UK*

Expert Opin. Drug Saf. (2009) 8(6):1-12

Case Study: Remacemide

Remacemide, an NMDA antagonist is developed as an antiepileptic

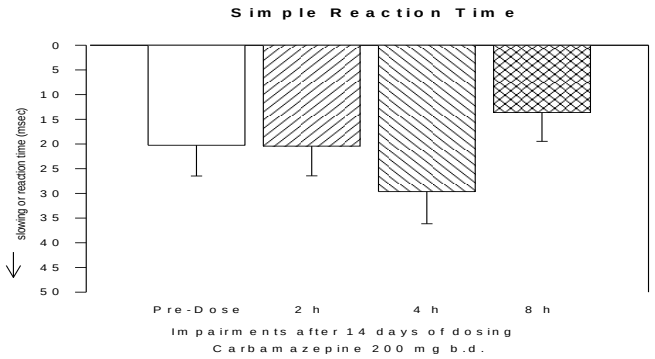
Series of Phase I trials with CDR system consistently show no negative cognitive effects of the compound. This suggests that in patients cognitive impairment and sedative effects should be uncommon.

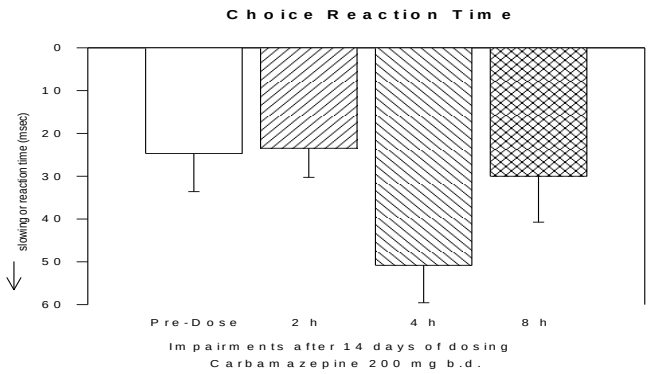
Wesnes K, Lockton A, Rolan P, Stephenson N, Pincock C. (1997). Volunteer study of the potential interaction between remacemide 300 mg and alcohol (0.7 g/kg). Journal of Psychopharmacology 11 Suppl.: A59.

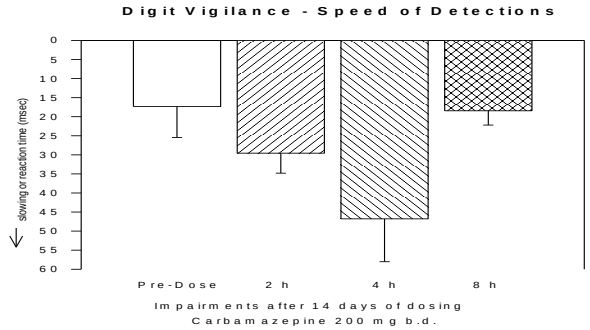
Lockton JA, Cole G, Hammersley M, Wesnes KA. (1998). Cognitive function is unaffected by remacemide at therapeutically relevant single doses. Journal of Psychopharmacology 12: Supplement A, A41.

Lockton JA, Wesnes KA, Yeates N, Rolan P, Diggory G. (1998). Remacemide does not affect cognitive function following multiple dosing. Journal of Psychopharmacology 12: Supplement A, A41.

Phase I Study
Cognitive Impairments due to 14 days Carbamazepine 200 mg BD in volunteers







Rapeport WG, Williams SA, Muirhead DC, Dewland PM, Tanner T, Wesnes K. (1996). Absence of a sertraline mediated effect on the pharmacokinetics and pharmacodynamics of carbamazepine. Journal of Clinical Psychiatry 57: 20 –23.

Epilepsy & Behavior 3, 140–146 (2002)
doi:10.1006/ebeh.2002.0337, available online at http://www.idealibrary.com on IDEAL®

Efficacy and Safety of Remacemide versus Carbamazepine in Newly Diagnosed Epilepsy: Comparison by Sequential Analysis

Martin J. Brodie, M.D.,*,1 Stephen J. Wroe, M.D.,†

TABLE 3
Most Frequently Reported Adverse Events

Adverse event	Remacemide (N = 288)	Carbamazepine (N = 282)
Headache	79 (27%)	72 (26%)
Dizziness	66 (23%)	48 (17%)
Somnolence	28 (10%)	55 (20%)
Fatigue	40 (14%)	56 (20%)
Nausea	56 (19%)	29 (10%)
Respiratory infection	35 (12%)	41 (15%)
Vomiting	37 (13%)	8 (3%)
Abdominal pain	34 (12%)	19 (7%)

Somnolence reported by only 10% of patients with remacemide compared to 20% with carbamazepine

Do opioid analgesics disrupt cognitive function in normals?

- Yes, clear cognitive impairment can be identified
- But not greater than with low doses of benzodiazepines
- If carefully monitored, moderate doses should not produce major deficits

Hanks GW (1995). Morphine sans Morpheus.

Lancet 34: 652-653.

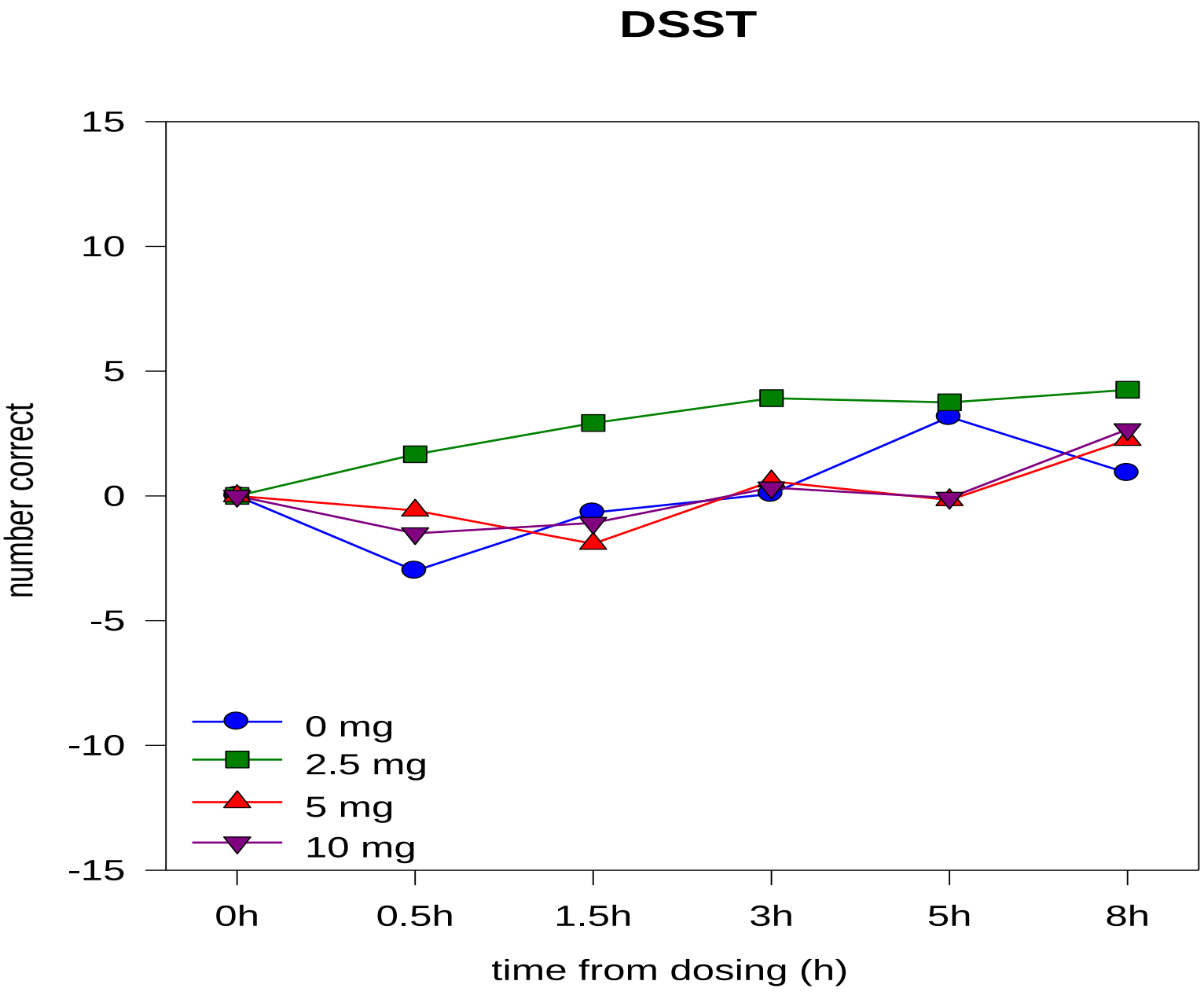
- But compounds free of cognitive impairment would be more desirable to patients

Case History

Question

- Can we identify a clinically relevant dose of morphine which will produce impairment in Phase I trials with around 12 volunteers?
- This can then act as a positive internal control for non-sedating opioids
- Trial conducted in AZ Phase I Unit, Stockholm
- Doses of morphine i.v. per 70 kg

Brooke C, Ehnhage A, Fransson B, Hägglöf B, Jonzon B, Kraft I, Wesnes K. (1998) The effects of intravenous morphine on cognitive function in healthy volunteers. Journal of Psychopharmacology 12: Supplement A, A45, 1998.


DSST
15
10
5
0
-5
-10
-15
number correct
0 mg
2.5 mg
5 mg
10 mg
0h
0.5h
1.5h
3h
5h
8h
time from dosing (h)

Amisulpride

Journal of Psychopharmacology 14(2) (2000) 164–171
©2000 British Association for Psychopharmacology (ISSN 0269-8811)
SAGE Publications, London, Thousand Oaks, CA and New Delhi
0269–8811[200006]14:2; 164–171; 013279

The acute effects of amisulpride (50 mg and 200 mg) and haloperidol (2 mg) on cognitive function in healthy elderly volunteers

E. Legangneux[1], J. McEwen[2], K. A. Wesnes[3], L. Bergougnan[1], N. Miget[1], M. Canal[1], C. L'Heritier[1], J. L. Pinquier[1] and P. Rosenzweig[1]

[1]Synthelabo Recherche, Bagneux, France, [2]DDS Medicines Research Ltd, Ninewells Hospital and Medical School, Dundee, Scotland and [3]Cognitive Drug Research Ltd, Reading, UK.

In this study, amisulpride could be differentiated from haloperidol, and at the high dose cognition enhancement was seen with amisulpride.

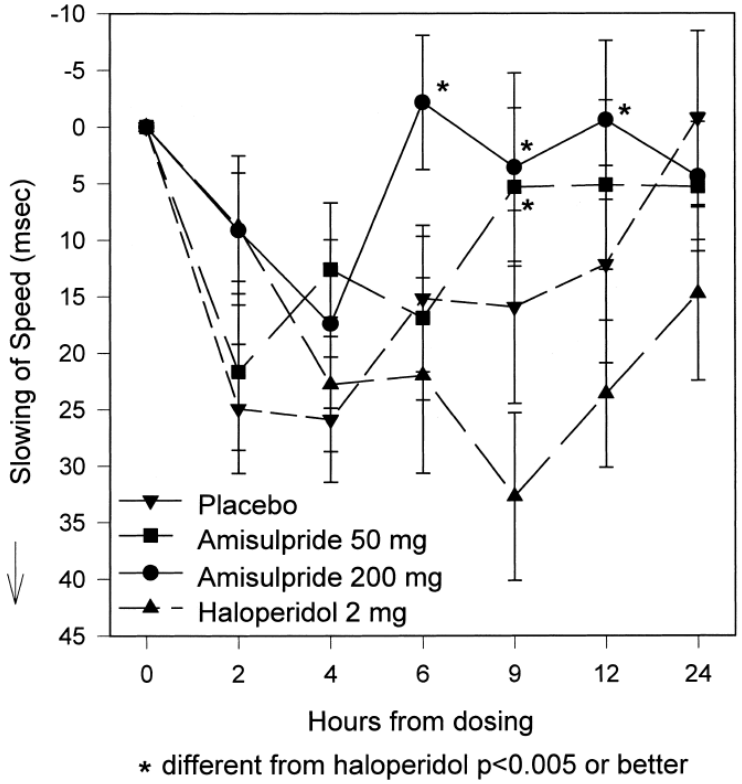


Figure 1 The effects of amisulpride, 50 mg and 200 mg, and haloperidol on the speed of detections in the digit vigilance task over the successive assessments of the study period. The data are adjusted for the pre-dosing baselines and expressed as mean ± SE

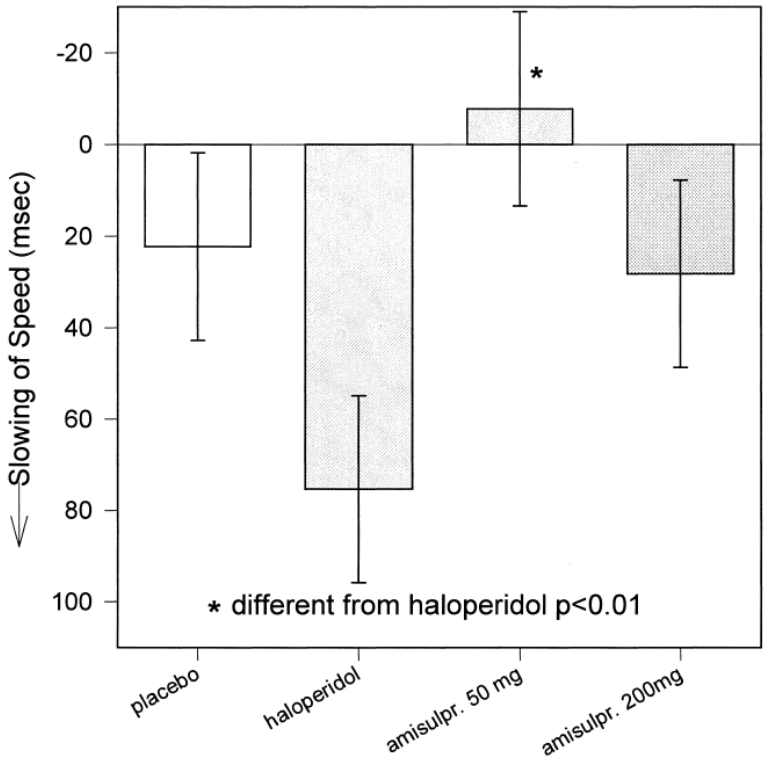


Figure 2 The effects of amisulpride, 50 mg and 200 mg, and haloperidol on the speed of accessing information from numeric working memory. The data are adjusted for the pre-dosing baselines and expressed as mean ± SE for the entire post-dosing period

Cognitive benefits in Phase I seen in Patients

Neuropsychopharmacology (2005) 30, 381–390
© 2005 Nature Publishing Group All rights reserved 0893-133X/05 $30.00
www.neuropsychopharmacology.org

Cognitive Improvement in Schizophrenic Patients does not Require a Serotonergic Mechanism: Randomized Controlled Trial of Olanzapine *vs* Amisulpride

Michael Wagner*[,1], Boris B Quednow[1], Jens Westheide[1], Thomas E Schlaepfer[1], Wolfgang Maier[1] and Kai-Uwe Kühn[1]

[1]*Department of Psychiatry, University of Bonn, Bonn, Germany*

Table 2 Neurocognitive Global and Domain *z*-Scores and Scores on Individual Neuropsychological Tests at Weeks 1, 4, and 8 (End Point)

	Amisulpride ($n = 18$)			Olanzapine ($n = 18$)		
	Week 1	Week 4	Week 8	Week 1	Week 4	Week 8
Measure	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Global cognitive index	0.06 (0.47)	0.28 (0.48)	0.30** (0.47)	−0.06 (0.72)	0.14 (0.52)	0.06‡ (0.49)
Neurocognitive domain scores						
Attention	−0.05 (0.53)	0.20 (0.57)	0.29** (0.56)	0.05 (0.67)	0.01 (0.47)	0.02 (0.44)
Executive functions	0.02 (0.56)	0.14 (0.48)	0.30** (0.40)	−0.02 (0.76)	0.17 (0.43)	0.10 (0.66)
Working memory	0.14 (0.62)	0.40 (0.58)	0.37** (0.57)	−0.14 (0.99)	0.23 (0.73)	0.18** (0.69)
Declarative memory	0.11 (0.62)	0.39 (0.74)	0.25‡ (0.76)	−0.11 (0.85)	0.14 (0.98)	−0.05 (0.94)

Case History

Question

Will olanzapine have a more favourable effect on cognitive function than haloperidol?

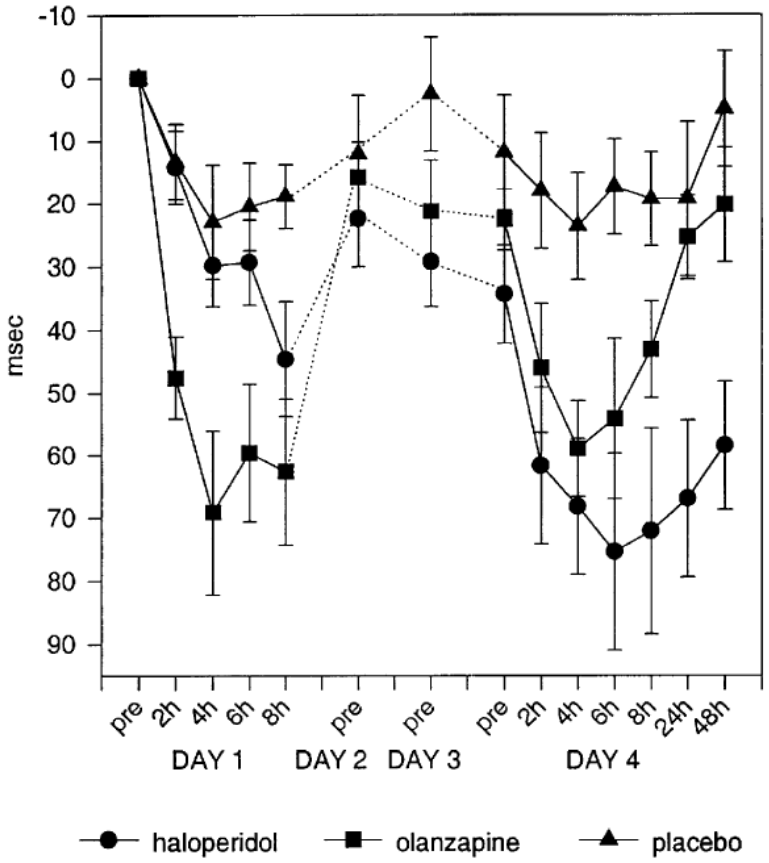
Journal of Psychopharmacology 13(2) (1999) 152–158
©1999 British Association for Psychopharmacology (ISSN 0269-8811)
SAGE Publications, London, Thousand Oaks, CA and New Delhi
0269-8811 [199905] 13:2; 152–158; 008440

A comparison of the effects of olanzapine, haloperidol and placebo on cognitive and psychomotor functions in healthy elderly volunteers

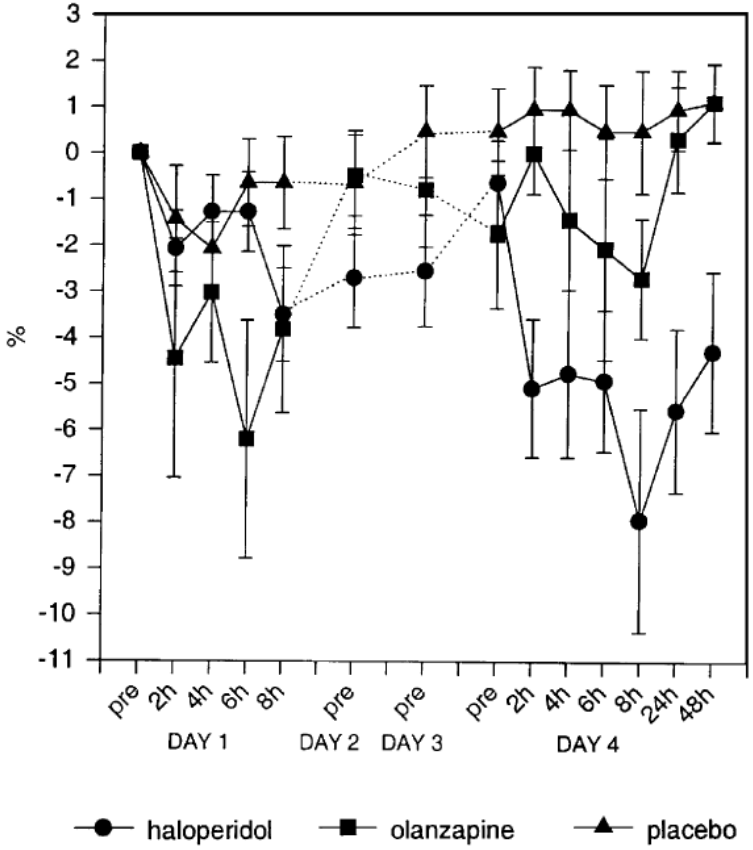
J-N. Beuzen[1], N. Taylor[1], K. Wesnes[2] and A. Wood[1]

[1]*Eli Lilly and Company Limited, Lilly Research Centre, Windlesham, Surrey and* [2]*Cognitive Drug Research Ltd, Priory Court, Reading, UK.*

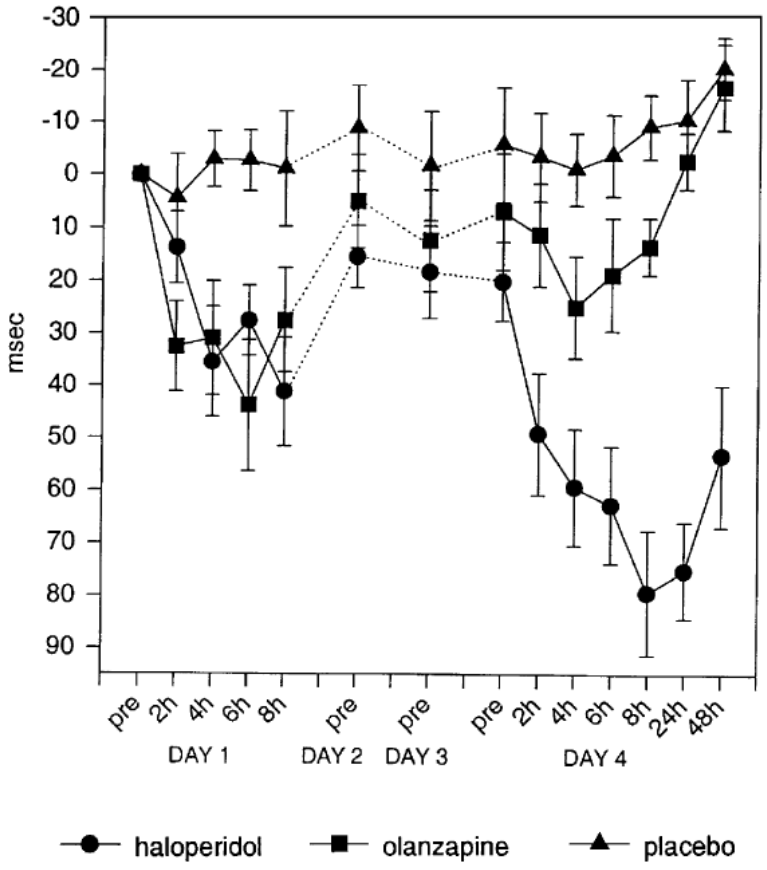
(a) Simple reaction time



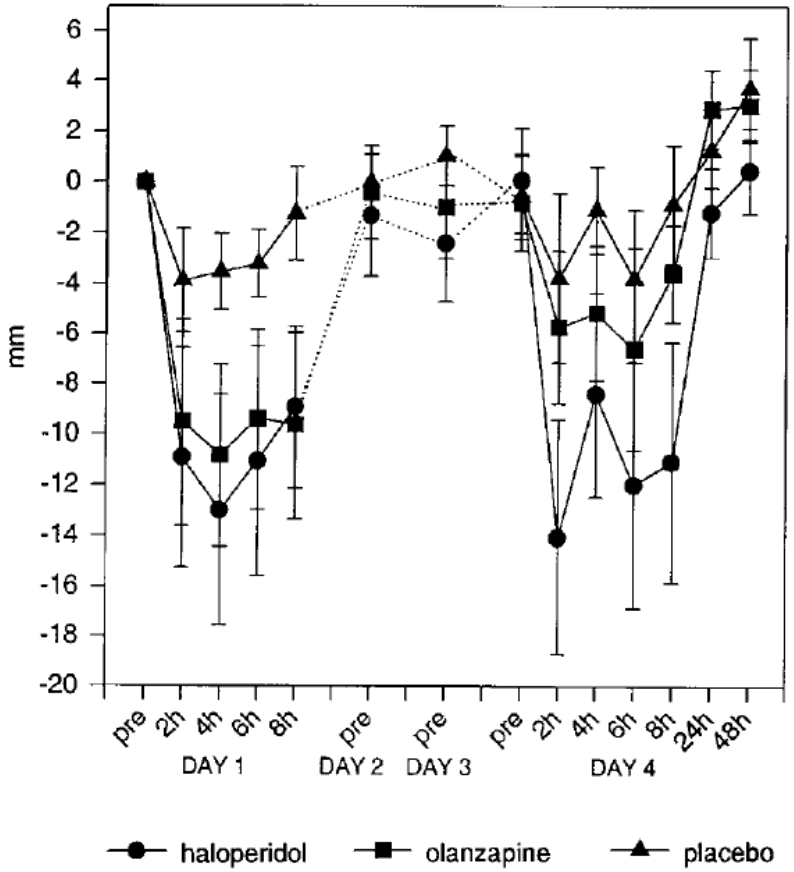
(c) Digit vigilance—accuracy



(b) Digit vigilance—speed



Subjective alertness

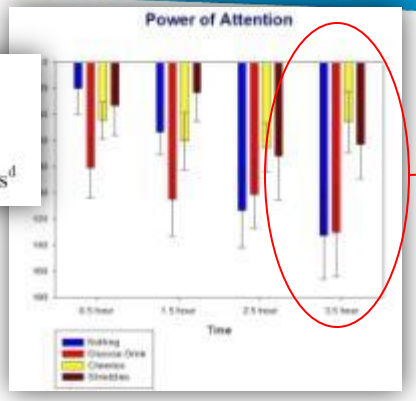


Non-Pharmaceuticals

Appetite 41 (2003) 329-331

Breakfast reduces declines in attention and memory over the morning in schoolchildren

Keith A. Wesnes[a],* Claire Pincock[a], David Richardson[b], Gareth Helm[c], Simon Hails[d]

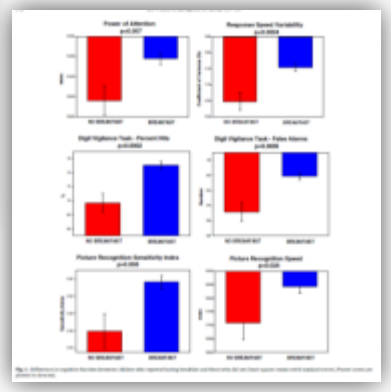


2003 CDR System study shows breakfast cereals outperform a glucose drink & no breakfast in helping sustain attentiveness & memory

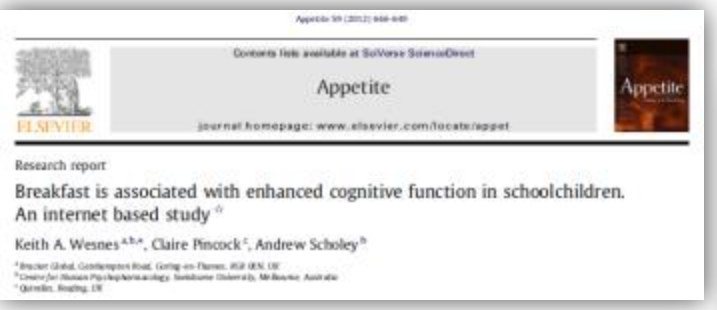
Data presented on Cereal packets

Nationwide internet study using CDR System in UK Government Breakfast Initiative

Study replicates laboratory results in 1386 children



After rejecting paper in 2006, same journal accepts unchanged version in 2012



Appetite 67 (2013) 105–113

Contents lists available at SciVerse ScienceDirect

Appetite

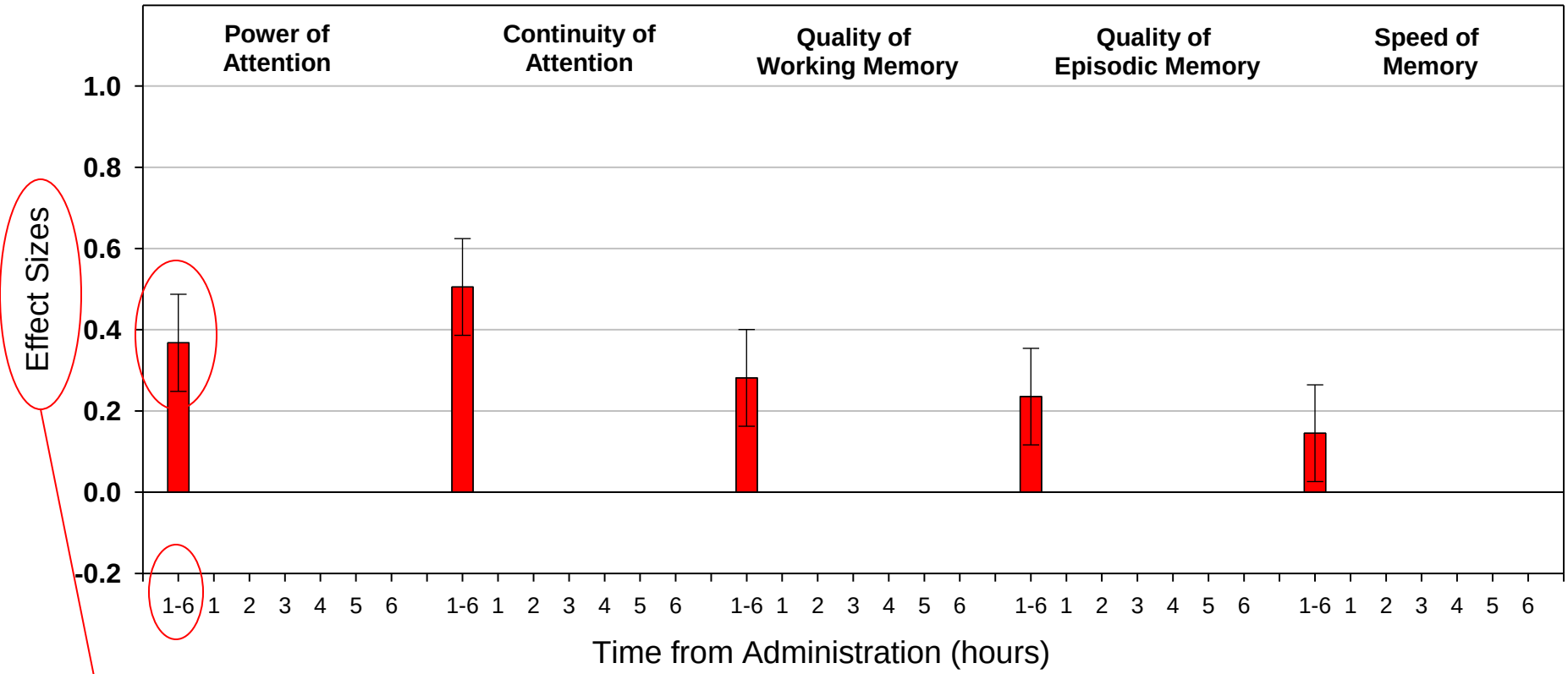
journal homepage: www.elsevier.com/locate/appet

Research report

An evaluation of the cognitive and mood effects of an energy shot over a 6 h period in volunteers. A randomized, double-blind controlled, cross-over study ☆

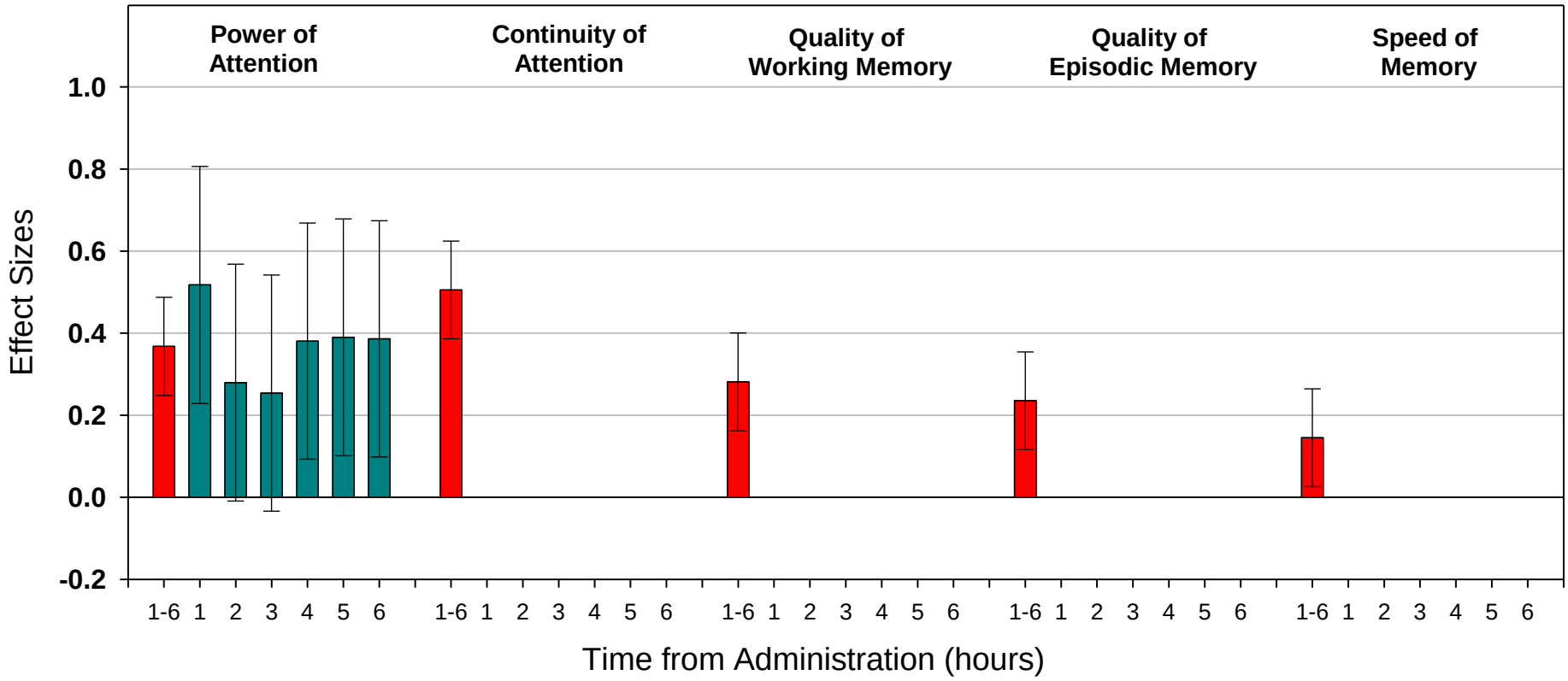
Keith A. Wesnes [a,b,*], Marilyn L. Barrett [c,d], Jay K. Udani [e,f]

CDR System Scores
Effect Sizes of Energy Shot compared to Placebo
With 95% Confidence Intervals

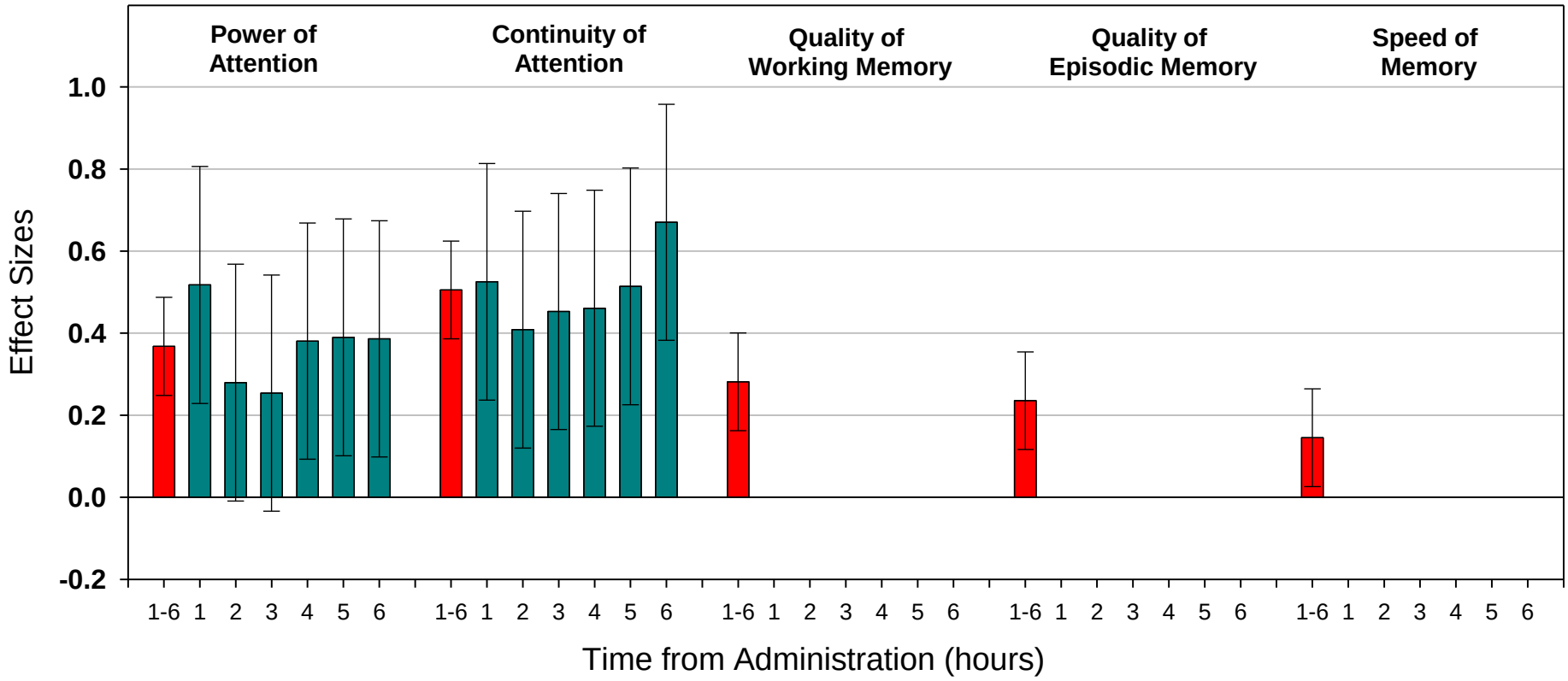


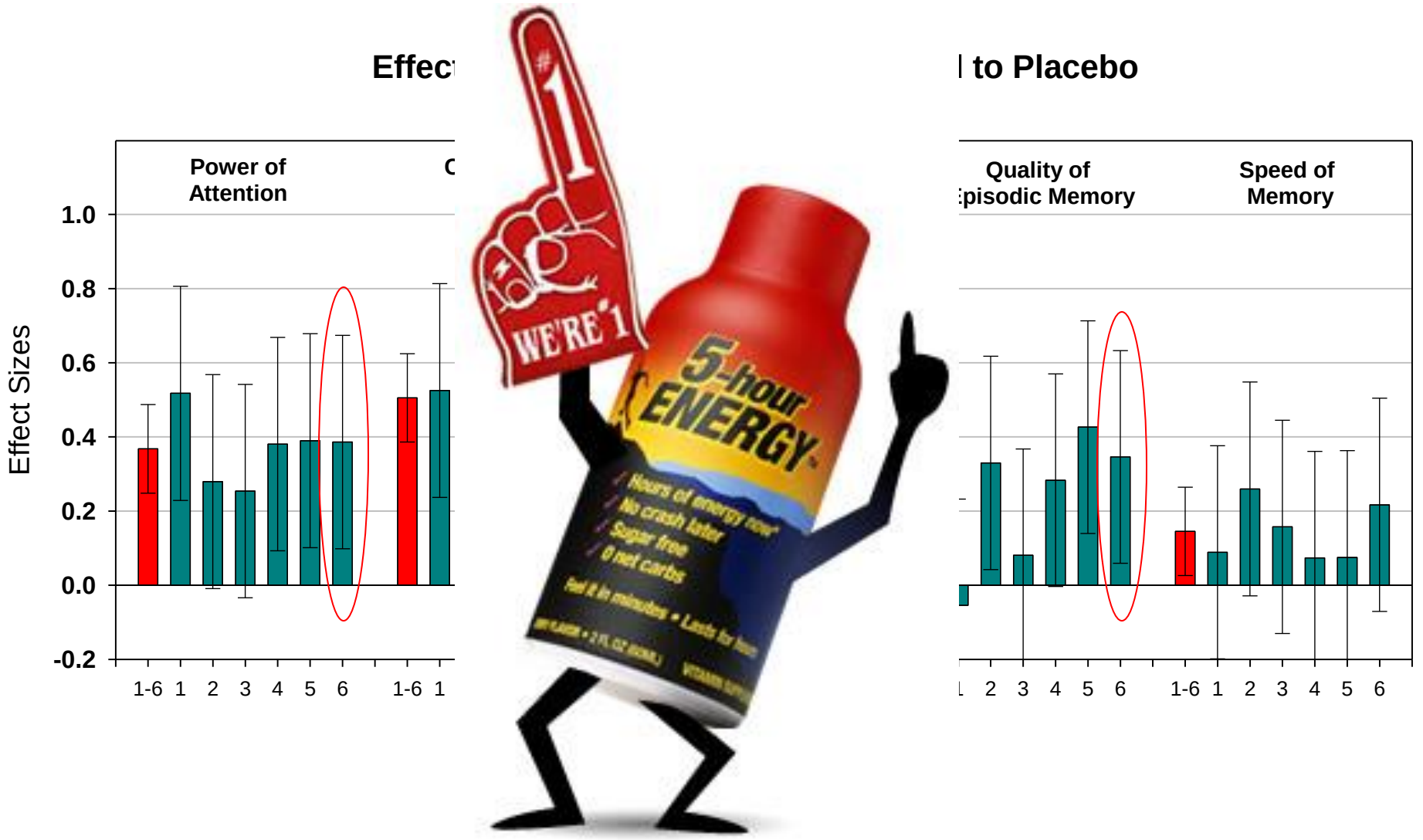
Improvements

CDR System Scores
Effect Sizes of Energy Shot compared to Placebo
With 95% Confidence Intervals

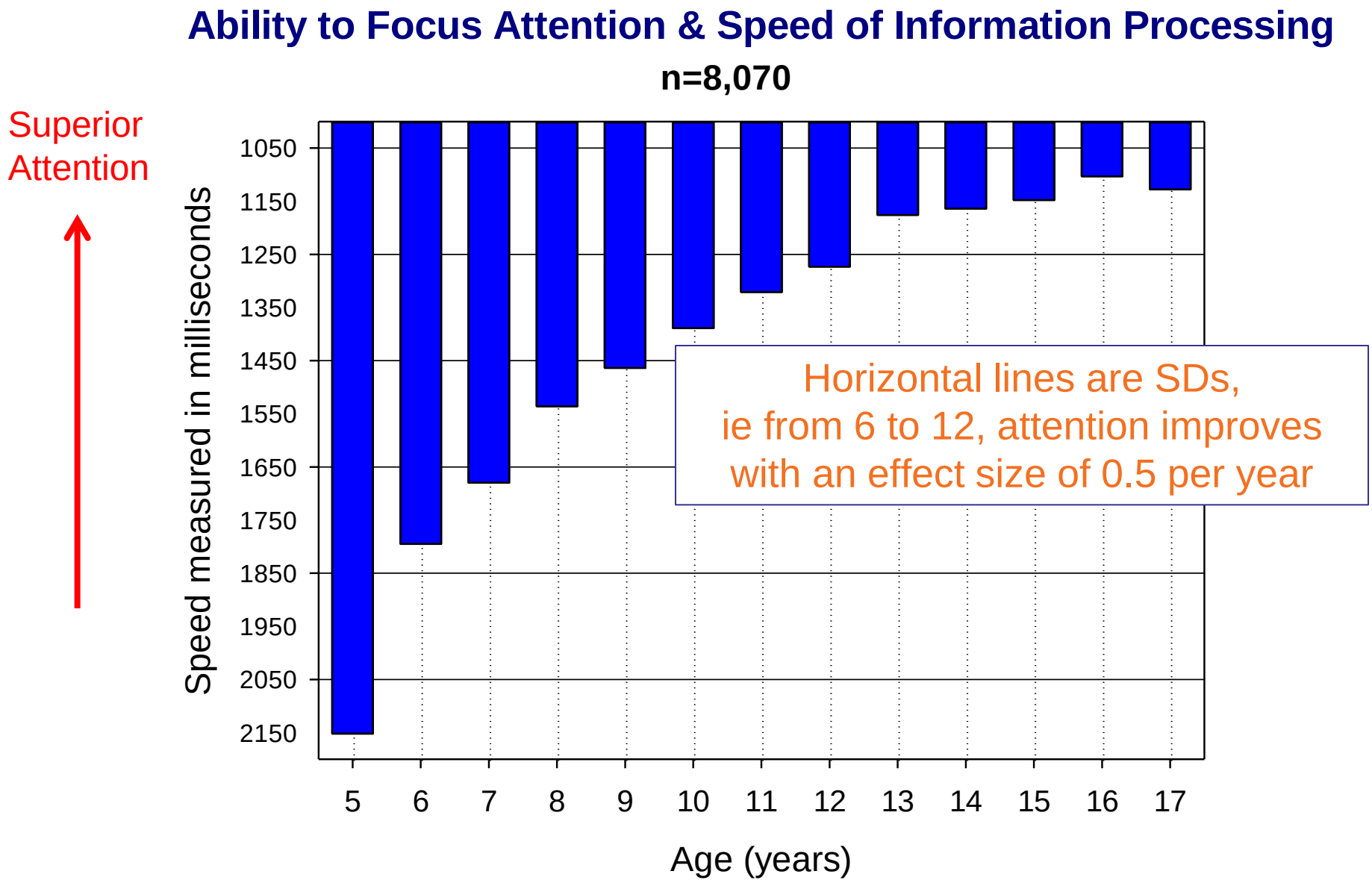


CDR System Scores
Effect Sizes of Energy Shot compared to Placebo
With 95% Confidence Intervals




Effec
to Placebo
Power of Attention
Quality of
pisodic Memory
Speed of Memory
Effect Sizes
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
1-6 1 2 3 4 5 6
1-6 1
1 2 3 4 5 6
1-6 1 2 3 4 5 6
#1
WE'RE 1
5-hour ENERGY
Hours of energy now
No crash later
Sugar free
0 net carbs

Year by year improvements in focussed attention and information processing



(The Journal of Neuropsychiatry and Clinical Neurosciences 2001; 13:326–335)

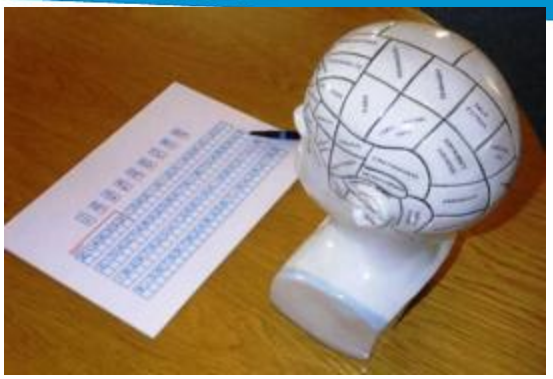
Effects of Stimulants on the Continuous Performance Test (CPT): Implications for CPT Use and Interpretation

Cynthia A. Riccio, Ph.D.
Jennifer J.M. Waldrop, M.S.
Cecil R. Reynolds, Ph.D.
Patricia Lowe, Ph.D.

Comparative Results Across Stimulants

A number of studies have compared the efficacy of the various stimulant medications on attention, as well as impulsivity, as measured by CPT performance. Based on Kavale's[51] meta-analysis, the mean effect sizes for MPH, dextroamphetamine, pemoline, and amphetamine (Benzedrine) were all moderate, ranging from 0.44 to 0.63.











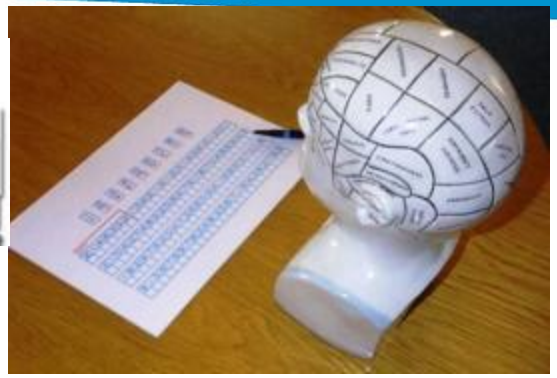



Donders Institute

AGENDA & NEWS | COLLABORATIONS | RESEARCH | GRADUATE SCHOOL | INFRASTRUCTURE | JOBS | ORGANIZ

F.C. Donders, the father of mental chronometry

"distraction during the appearance of the stimulus is always punished with prolongation of the process" (1868).



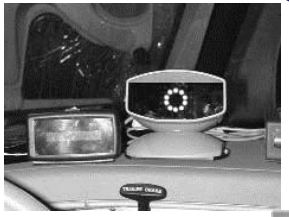
Brief Assessment of Cognition in Schizophrenia (BACS)*

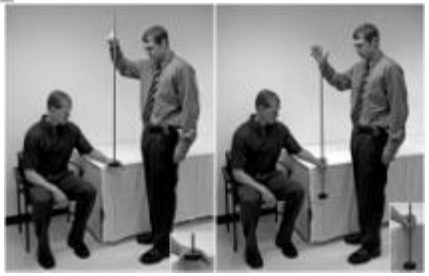
- Includes 6 tests that measure 6 cognitive domains
- Approximately 30 min to administer
- Composite score has high test-retest reliability in patients with schizophrenia

NeuroCog

Cognitive Domain	Test
Motor speed	Token Motor Task
Attention and processing speed	Symbol Coding
Working memory	Digit Sequencing Task
Verbal memory	List Learning
Verbal fluency	Tests of Category Instances and Controlled Oral Word Association Test
Reasoning and problem solving	Tower of London

*Keefe et al., Schiz Res (2004)





Regulatory Experience

Labelling

- Compounds for which Phase I data from safety, PK/PD, Alcohol or Drug-Drug interaction trials have been used to support product labelling:
  - Fluvoxamine
  - Mirtazapine
  - Moxonidine
  - Olanzapine
  - Sertaline
  - Sibutramine
  - Tiagabine
  - Tizanidine

CDR System confirms absence of alcohol interaction with sibutramine which is included in labelling

Effects of sibutramine alone and with alcohol on cognitive function in healthy volunteers

K. A. Wesnes,[1] C. Garratt,[2] M. Wickens,[2] A. Gudgeon[1] & S. Oliver[3]

[1]*Cognitive Drug Research Limited, Reading,* [2]*Knoll Pharmaceuticals, Nottingham and* [3]*Covance Clinical Research Unit, Leeds, UK*

Conclusions There was little evidence of a clinically relevant interaction of sibutramine with the impairment of cognitive function produced by alcohol in healthy volunteers. The single statistically significant interaction indicated a reduction, rather than a worsening, of alcohol-induced impairment when sibutramine is taken concomitantly. Sibutramine when administered alone is associated with improved performance on several tasks.

© 2000 Blackwell Science Ltd *Br J Clin Pharmacol*, **49**, 110–117

CDR System data on absence on interaction of sibutramine with alcohol

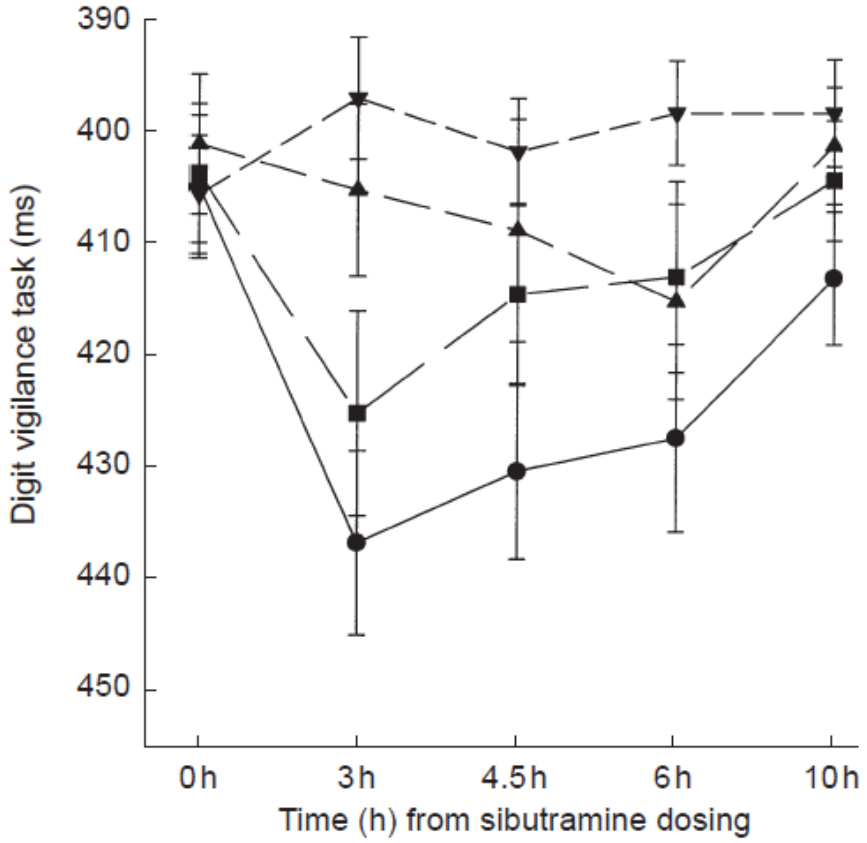


Figure 1 The speed of detections in the digit vigilance task (ms): illustration of the observed treatment effects (means ± s.e. mean) over the time. ▲ placebo, ▼ sibutramine alone, ● alcohol alone, ■ alcohol + sibutramine.

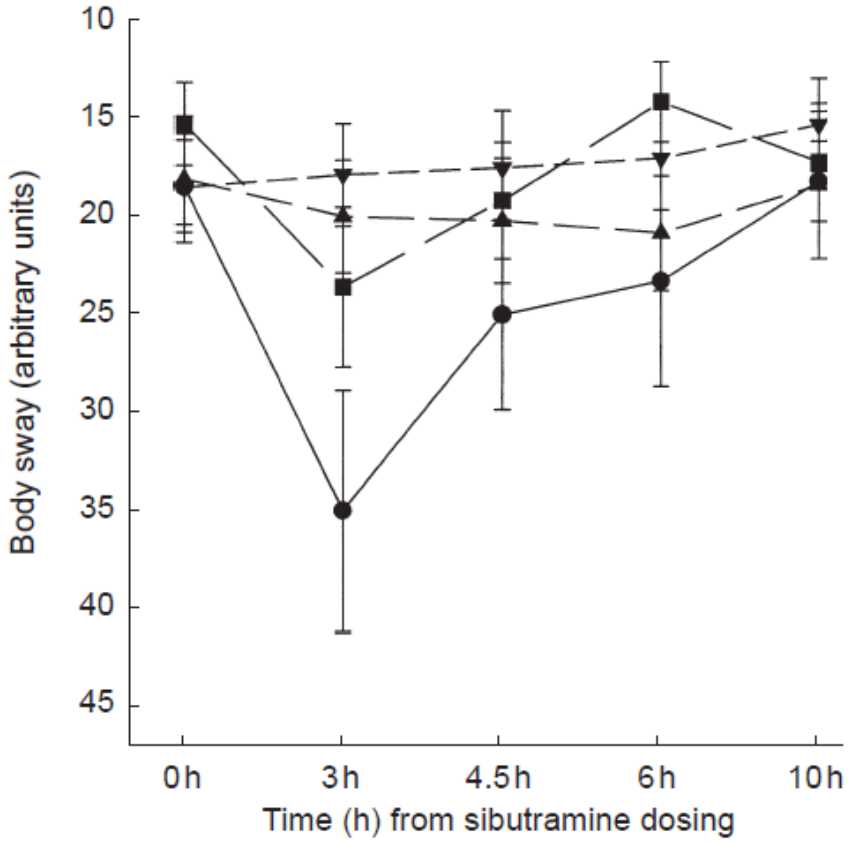


Figure 2 Body sway (arbitrary units): illustration of the observed treatment effects (mean ± s.e. mean) over the time course of the study days. ▲ placebo, ▼ sibutramine alone, ● alcohol alone, ■ alcohol + sibutramine.

Results of this study used in labelling for Meridia (Sibutramine)

- http://www.fda.gov/downloads/Drugs/DrugSafety/PublicHealthAdvisories/UCM130745.pdf

MERIDIA®

(sibutramine hydrochloride monohydrate) Capsules

CS-IV

Alcohol

In a double-blind, placebo-controlled, crossover study in 19 volunteers, administration of a single dose of ethanol (0.5 mL/kg) together with 20 mg of sibutramine resulted in no psychomotor interactions of clinical significance between alcohol and sibutramine. However, the concomitant use of MERIDIA and excess alcohol is not recommended.

CDR System confirms absence of alcohol interaction with fluvoxamine which is included in labelling

Fluvoxamine does not interact with alcohol or potentiate alcohol-related impairment of cognitive function

Objective: To assess whether fluvoxamine alters the pharmacokinetics of alcohol or potentiates alcohol-related impairment of cognitive function.
Methods: The study design required partially "blinded" balanced crossover studies, each involving 12 healthy male volunteers who each received a 40 gm dose of intravenous or oral alcohol after single and multiple doses of 50 mg fluvoxamine. Main outcome measures for pharmacokinetics were venous blood alcohol and plasma fluvoxamine. Main outcome measures for pharmacodynamics were word recall, simple and choice reaction time, number vigilance, memory scanning, and word recognition.
Results: The pharmacokinetics of intravenous alcohol were not affected by concomitant administration of fluvoxamine. Compared with placebo-alcohol, alcohol slightly increased the rate of fluvoxamine absorption, but the area under the plasma concentration–time curve from 0 to 12 hours at steady state was unchanged. As expected, alcohol significantly impaired cognitive function in volunteers. However, fluvoxamine did not potentiate the effects of alcohol and in some instances appeared to reverse the effects or reduce their duration. Fluvoxamine was well tolerated: only mild adverse effects were reported, and none of those required intervention.
Conclusion: Fluvoxamine does not interact significantly with alcohol or potentiate alcohol-related impairment of cognitive function. (CLIN PHARMACOL THER 1992;52:427-35.)

Jaap van Harten, PhD, Lloyd A. Stevens, PhD, Maikel Raghoebar, PhD,
Robert L. Holland, MD, PhD, Keith Wesnes, PhD, and Antoine Cournot, MD
Weesp, The Netherlands, Leeds and Reading, England, and Boulogne-Billancourt, France

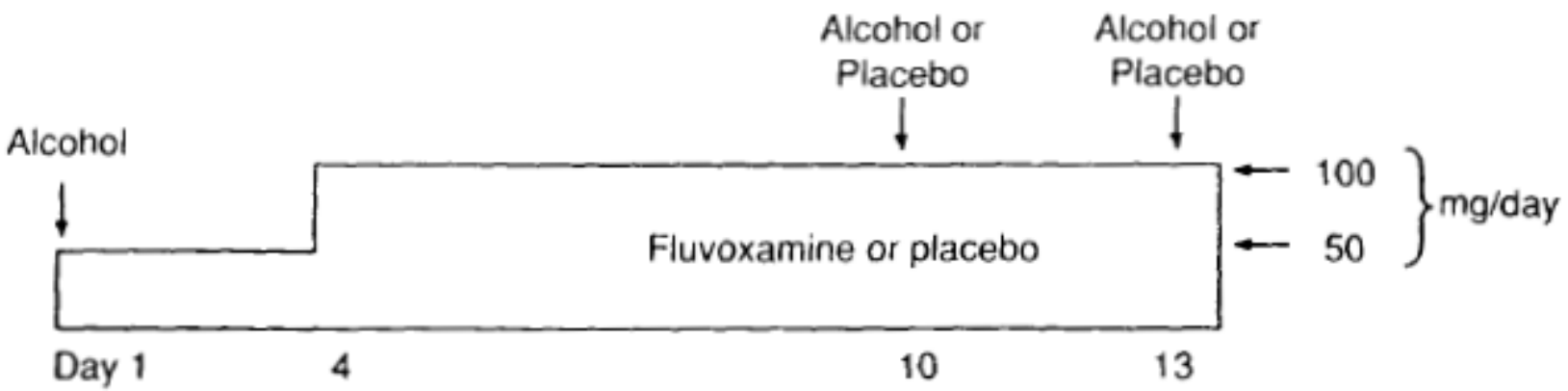


Fig. 2. Study 2: Schematic representation of administration schedules for oral alcohol and oral placebo-alcohol and for fluvoxamine and placebo in healthy volunteers.

Table I. Effect of single and multiple doses of fluvoxamine on the C_{max} and AUC(0-8) of alcohol after an intravenous dose of 40 gm

Ratio	C_{max}		*AUC(0-8)*	
	*Mean**	*90% Confidence limits*	*Mean**	*90% Confidence limits*
Single dose/placebo	1.10	1.01-1.21	1.07	0.98-1.16
Multiple dose/placebo	0.96	0.87-1.05	0.95	0.88-1.03

C_{max}, Peak plasma concentration; AUC(0-8), area under the concentration-time curve.
*Treatment mean values are expressed as the ratio of fluvoxamine to placebo.

Results: The pharmacokinetics of intravenous alcohol were not affected by concomitant administration of fluvoxamine. Compared with placebo-alcohol, alcohol slightly increased the rate of fluvoxamine absorption, but the area under the plasma concentration–time curve from 0 to 12 hours at steady state was unchanged. As expected, alcohol significantly impaired cognitive function in volunteers. However, fluvoxamine did not potentiate the effects of alcohol and in some instances appeared to reverse the effects or reduce their duration. Fluvoxamine was well tolerated: only mild adverse effects were reported,

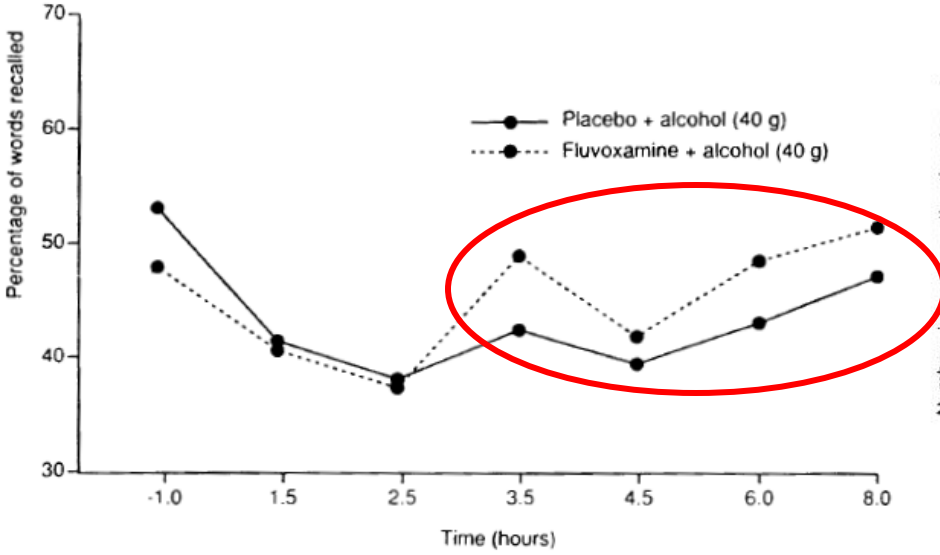


Fig. 3. Mean percentage of words recalled after concomitant administration of single doses of 50 mg fluvoxamine or placebo and 40 gm alcohol in healthy volunteers.

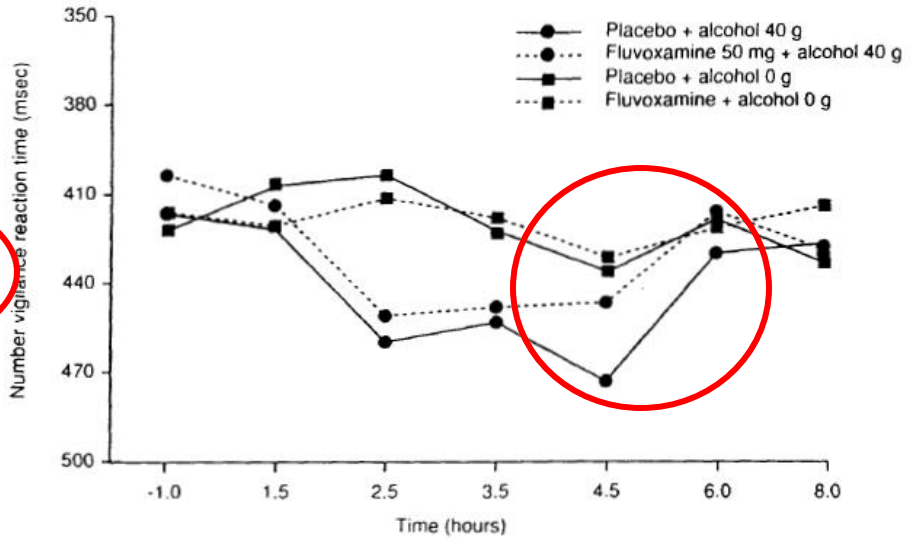


Fig. 5. Mean number vigilance reaction time after concomitant administration of multiple doses of 50 mg fluvoxamine or placebo and 40 gm alcohol or placebo-alcohol in healthy volunteers.

LUVOX CR® (Fluvoxamine Maleate) Extended-Release Capsules

Highlights of Prescribing Information
These highlights do not include all the information needed to use LUVOX CR® (Fluvoxamine Maleate) Extended-Release Capsules safely and effectively. See full prescribing information for LUVOX CR Capsules.

LUVOX CR® (Fluvoxamine Maleate) Extended-Release Capsules for oral administration
Initial U.S. Approval: 2008

Alcohol: Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with immediate-release fluvoxamine maleate tablets (50 mg given twice daily) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other. As with other psychotropic medications, patients should be advised to avoid alcohol while taking LUVOX CR Capsules.

Carbamazepine: Elevated carbamazepine levels and symptoms of toxicity have been reported with the coadministration of immediate-release fluvoxamine maleate tablets and carbamazepine.

Clozapine: See ***WARNINGS AND PRECAUTIONS*** *(5.8)*.

Ability of CDR System to confirm differential PK profiles & Impact on FDA labelling

Clinical Therapeutics/Volume 28, Number 9, 2006

Effects of Food on the Single-Dose Pharmacokinetics/ Pharmacodynamics of Tizanidine Capsules and Tablets in Healthy Volunteers

Jaymin Shah, PhD[1]*; Keith A. Wesnes, PhD[2]; Rosemary A. Kovelesky, RPh, PhD[1]†; and Herbert R. Henney III, PharmD[3]

[1]Elan Pharmaceuticals, Inc., San Diego, California; [2]Cognitive Drug Research Ltd., Goring-on-Thames, United Kingdom; Chiron Corporation, Emeryville, California; and [3]Acorda Therapeutics, Inc., Hawthorne, New York

Relating PK & PD

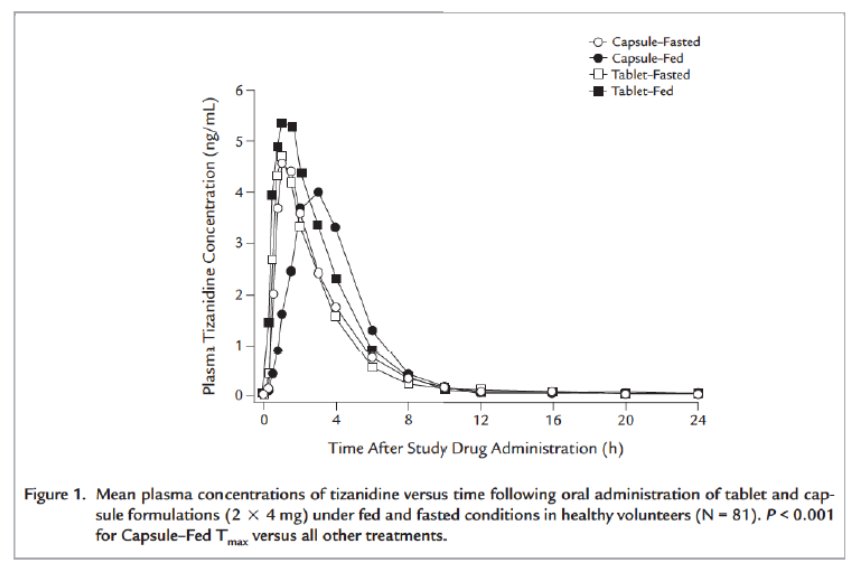


Figure 1. Mean plasma concentrations of tizanidine versus time following oral administration of tablet and capsule formulations (2 × 4 mg) under fed and fasted conditions in healthy volunteers (N = 81). $P < 0.001$ for Capsule–Fed T_{max} versus all other treatments.

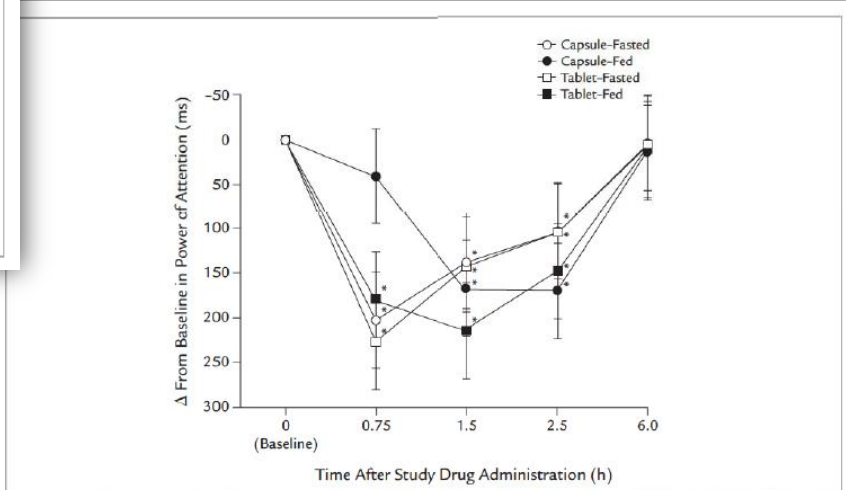
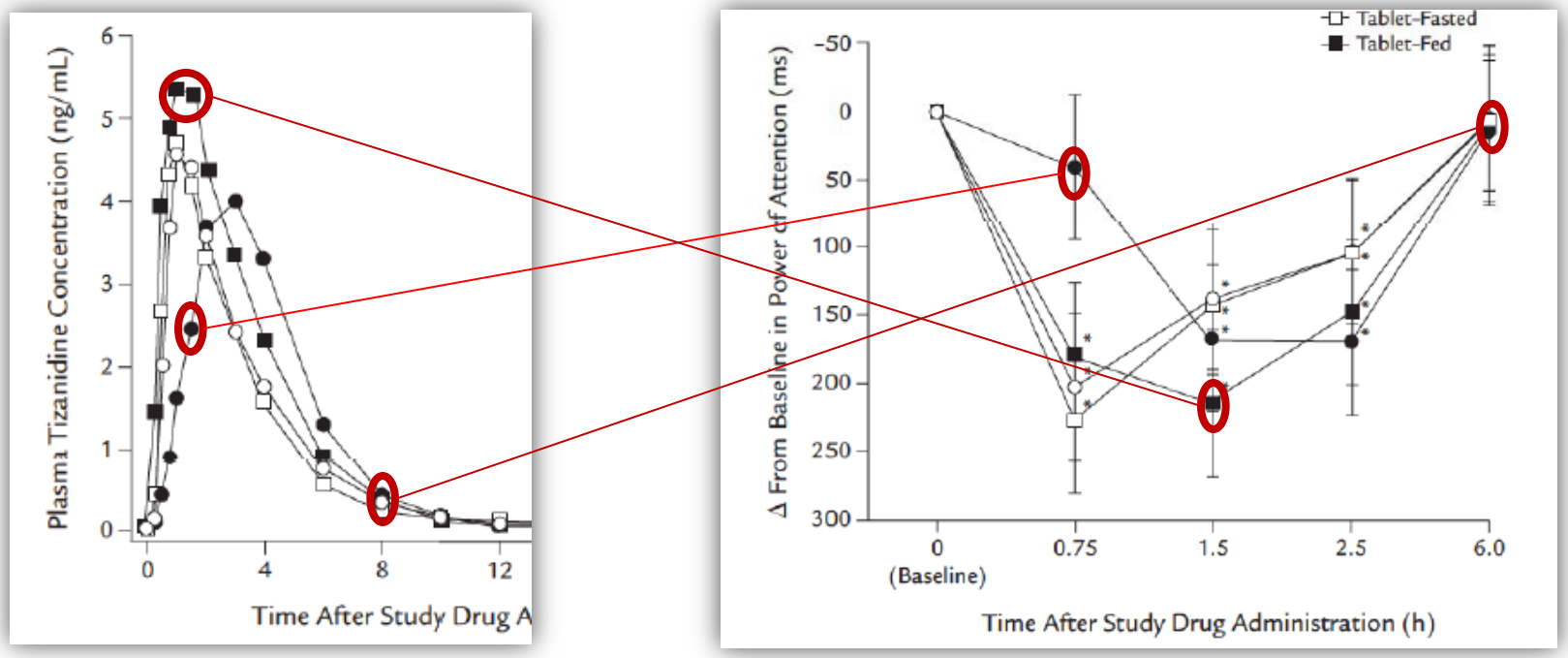


Figure 2. Mean change from baseline in Power of Attention versus time following oral administration of tablet and capsule formulations (2 × 4 mg) under fed and fasted conditions in healthy volunteers (N = 88). Power of Attention[26] reflects overall ability to focus and sustain attention. *$P < 0.001$ versus baseline.

Shah J, Wesnes KA, Kovelesky RA, Henney HR (2006) Effects of food on the single-dose pharmacokinetics/pharmacodynamics of Tizanidine capsules and tablets in healthy volunteers. Clinical Therapeutics 28: 1308-1317.

Relationship of PK to PD effects



Shah J, Wesnes KA, Kovelesky RA, Henney HR (2006) Effects of food on the single-dose pharmacokinetics/pharmacodynamics of Tizanidine capsules and tablets in healthy volunteers. Clinical Therapeutics 28: 1308-1317.

CDR System Data Convinced FDA to Alter Labelling

CONCLUSIONS

The results of this study suggest that tizanidine appears generally well tolerated in healthy men and women who received tablets and capsules in the fed and fasted conditions. However, tizanidine impaired cognitive function and lowered self-rated alertness. These effects were found from 0.75 to 2.5 hours after tablets were administered with or without food and after capsules were administered under fasted conditions. Overall, there was a significantly lower AE rate observed with the capsules compared to tablets regardless of food use. The effect of food on the increase in C_{max} and AUC of tizanidine found with the commercial tablet was diminished with the multiparticulate capsule formulation. Based on the results of this study, the FDA considered these differences sufficient not to give an A/B rating to the capsule. As a result of the prolonged T_{max}, with the capsule, there was a delay in the onset of cognitive impairment from 0.75 hour to 1.5 hours postdose. By 6 hours, all effects had passed for all treatment regimens.

Based on the results of this study, the FDA considered these differences sufficient not to give an A/B rating to the capsule.

Drug – Drug Interaction Studies

Series of drug-drug interaction trials with sertraline in registration programme:

Clear effects of carbamazepine, phenytoin and haloperidol detected but no evidence of interactions with sertraline

- Rapeport WG, Williams SA, Muirhead DC, Dewland PM, Tanner T, Wesnes K. (1996). Absence of a sertraline mediated effect on the pharmacokinetics and pharmacodynamics of carbamazepine. Journal of Clinical Psychiatry 57: 20 –23.
- Rapeport WG, Muirhead DC, Williams SA, Cross M, Wesnes K (1996). Absence of effect of sertraline on the pharmacokinetics and pharmacodynamics of phenytoin. Journal of Clinical Psychiatry 57: 24-28,
- Williams SA, Wesnes K, Oliver SD, Rapeport WG (1996). Absence of effect of sertraline on time based sensitisation of cognitive impairment with haloperidol. Journal of Clinical Psychiatry 57: 7-11 , 1996

Two drug-drug interaction trials run in registration programme of moxonidine, used in labelling.

Eur J Clin Pharmacol (1997) 52: 351–358

PHARMACODYNAMICS

K. Wesnes · P. M. Simpson · B. Jansson · A. Grahnén
H-J. Weimann · H. Küppers

Moxonidine and cognitive function: interactions with moclobemide and lorazepam

Interactions of moxonidine with lorazepam on CDR attention tasks

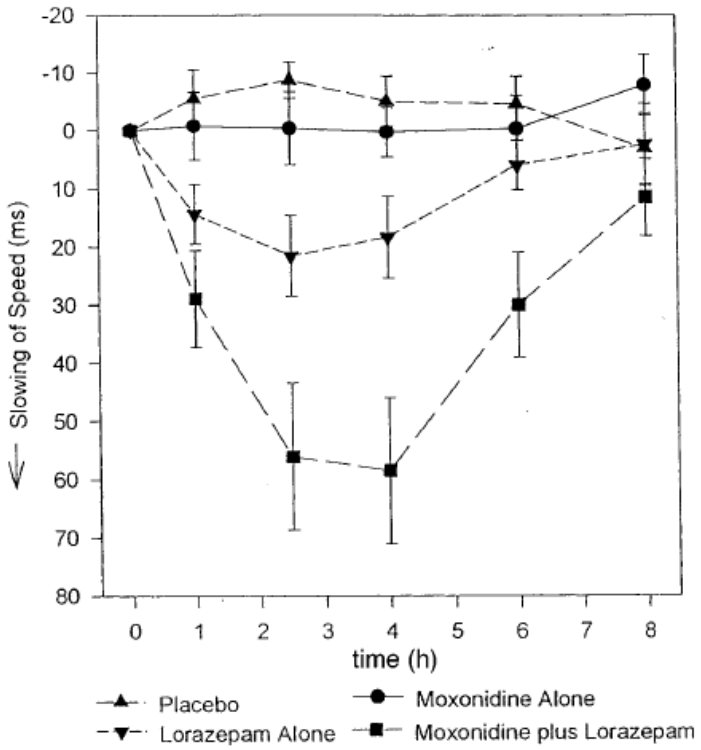


Fig. 1 The group means (SEM) of the four dosing conditions over time in study 2 for speed on the choice reaction time task

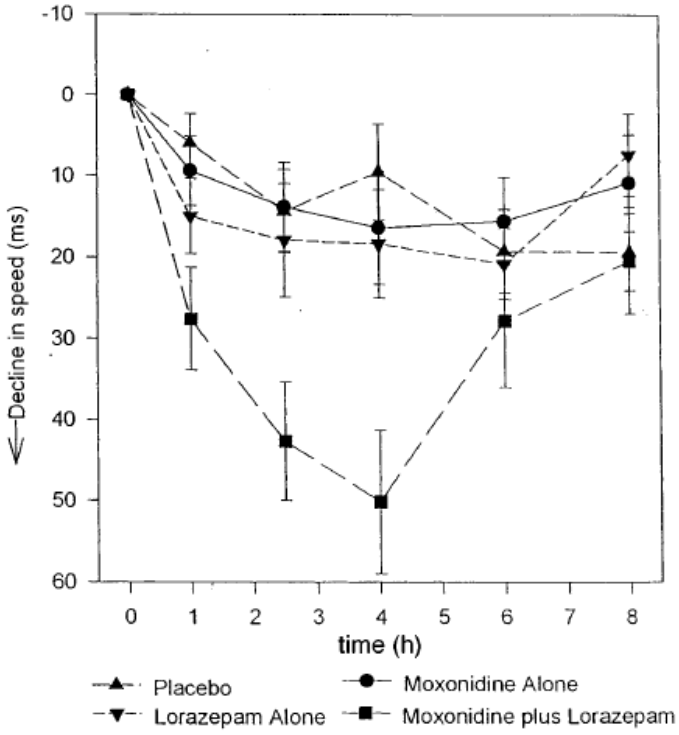


Fig. 2 The group means (SEM) of the four dosing conditions over time in study 2 for speed of detections on the digit vigilance task

Interaction of moxonidine with lorazepam on CDR tracking task but selective, no effects on episodic memory assessed on delayed recall

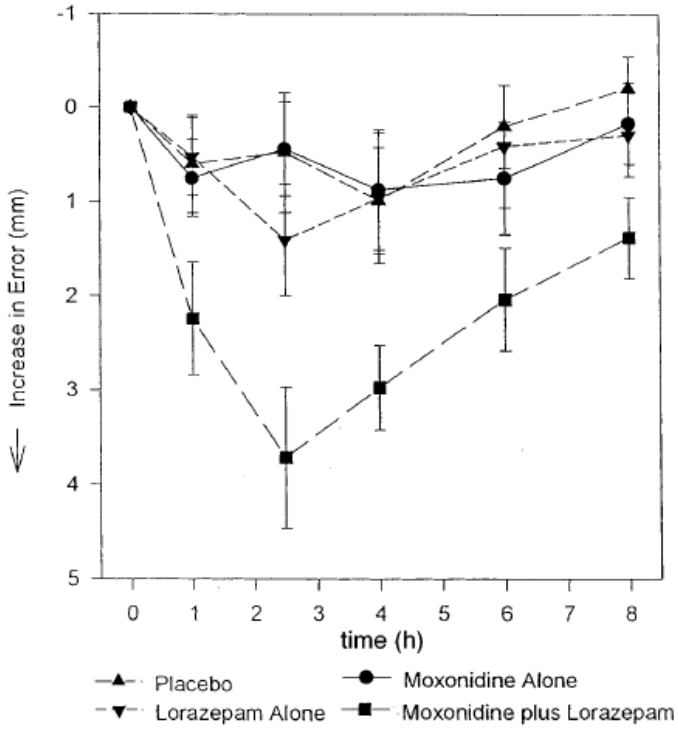


Fig. 4 The group means (SEM) of the four dosing conditions over time in study 2 for the average distance off-target on the visual tracking task

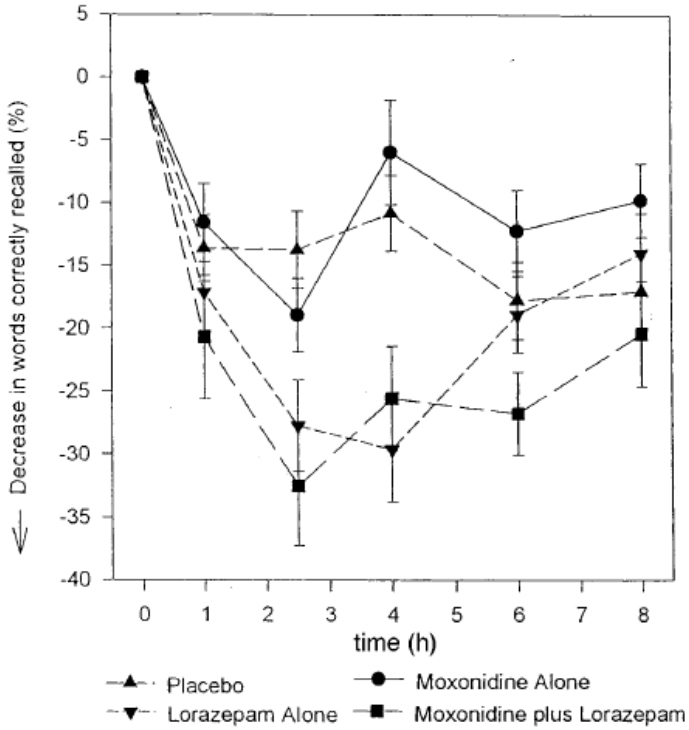


Fig. 6 The group means (SEM) of the four dosing conditions over time in study 2 for the words recalled correctly in the delayed recall task

Conclusions

- Interactions were identified with lorazepam 1 mg but not moclobemide
- However a previous issue of this Journal contained a paper showing the effects of lorazepam 2 mg on the CDR System.
- This enabled the interaction to be put into context in the paper:
  - "…the increased impairments are still less than would be produced by a doubling of this dose of lorazepam. This is not to state that such potentiation will not lead to everyday attentional problems, but it does provide a reference point for the amount of extra disruption experienced. (page 357)"

ELSEVIER

A Pharmacokinetic and Pharmacodynamic Drug Interaction Study of Acamprosate and Naltrexone

Barbara J. Mason, Ph.D., Anita M. Goodman, M.D., Russell M. Dixon, M.D., Magdy H. Abdel Hameed, Ph.D., Thierry Hulot, Pharm.D., Keith Wesnes, Ph.D., John A. Hunter, M.S., and Michael G. Boyeson, Ph.D.

[Neuropsychopharmacology 27:596–606, 2002]
© 2002 *American College of Neuropsychopharmacology.*
Published by Elsevier Science Inc.

No evidence of interaction from CDR data

Table 2. Within Subjects Change from Baseline on Each Test of Cognitive Function in Each Treatment Condition (N=24)*

	Acamprosate	Naltrexone	Acamprosate and Naltrexone
Simple Reaction Time	17.4 ± 3.5	15.5 ± 3.5	21.9 ± 3.5
Choice Reaction Time (msec)	6.4 ± 3.7	22.5 ± 3.7[a,b]	10.2 ± 3.7
Digit Vigilance			
Accuracy (%)	−1.16 ± 0.4	−0.4 ± 0.4	−0.0 ± 0.4
Speed (msec)	9.6 ± 2.4	17.5 ± 2.4[a,b]	8.1 ± 2.4
Numeric Working Memory			
Sensitivity Index	−0.03 ± 0.1	−0.05 ± 0.1	−0.05 ± 0.1
Speed (msec)	−10.4 ± 6.5	6.9 ± 6.5	−2.2 ± 6.5
Immediate Word Recall-Accuracy (%)	−3.0 ± 0.9[c]	0.3 ± 0.9	−1.4 ± 0.9
Delayed Word Recall-Accuracy (%)	−1.6 ± 1.0	−2.5 ± 1.0	−2.1 ± 1.0
Delayed Word Recognition			
Sensitivity Index	−0.03 ± 0.01	−0.07 ± 0.01[a,b]	−0.00 ± 0.01
Speed (msec)	−37.7 ± 7.6[b,c]	−2.3 ± 7.6	−7.0 ± 7.6

*Values given are least squares means ± standard error of the mean. An ANOVA was applied to each cognitive measure and when the main effect of treatment condition was significant, the least squares means procedure was used to make multiple comparisons between treatment conditions to identify where the significant differences lay.

[a] $p < .05$ vs. acamprosate alone

[b] $p < .05$ vs. acamprosate and naltrexone combined

[c] $p < .05$ vs. naltrexone alone

HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2001; **16**: 449–459.
DOI: 10.1002/hup.318

Mirtazapine and paroxetine: a drug-drug interaction study in healthy subjects

F. J. L. Ruwe[1], R. A. Smulders[3], H. J. Kleijn[2], H. L. A. Hartmans[3] and J. M. A. Sitsen[1]*

[1]*Clinical Development Department, NV Organon, PO Box 20, 5340 BH Oss, The Netherlands*
[2]*Department of Drug Metabolism & Kinetics, NV Organon, PO Box 20, 5340 BH Oss, The Netherlands*
[3]*Kendle (formerly U-Gene Research BV) Clinical Pharmacology Unit, Bolognalaan 40, 3584 CJ Utrecht, The Netherlands*

EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS 2001, Vol. 26, No. 1/2, pp. 109-121

Drug-drug interaction studies with mirtazapine and carbamazepine in healthy male subjects

JMA SITSEN, FA MARIS, CJ TIMMER
N.V. Organon Oss, The Netherlands

Received for publication: 20 October 2000

Key words: mirtazapine, enzyme induction, carbamazepine, pharmacokinetics

Journal of Psychopharmacology 14(2) (2000) 172–176
©2000 British Association for Psychopharmacology (ISSN 0269-8811)
SAGE Publications, London, Thousand Oaks, CA and New Delhi
0269–8811[200006]14:2; 172–176; 013280

Pharmacokinetics of mirtazapine and lithium in healthy male subjects

J. M. A. Sitsen[1], G. Voortman[2] and C. J. Timmer[2]

[1]Clinical Development Department and [2]Department of Drug Metabolism and Kinetics, NV Organon, The Netherlands.

Evidence of interaction between melatonin and zolpidem

HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2008; **23**: 693–705.
Published online 2 September 2008 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.980

Effects of prolonged-release melatonin, zolpidem, and their combination on psychomotor functions, memory recall, and driving skills in healthy middle aged and elderly volunteers

S. Otmani[1]*, A. Demazières[1], C. Staner[1], N. Jacob[1], T. Nir[2], N. Zisapel[2,3] and L. Staner[1]

[1]*FORENAP – Institute for Research in Neurosciences, Rouffach, France*
[2]*Neurim Pharmaceuticals Ltd., Tel-Aviv, Israel*
[3]*Department of Neurobiochemistry, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel*

No effects of melatonin alone, but interaction seen to Power of Attention when co-dosed with melatonin.

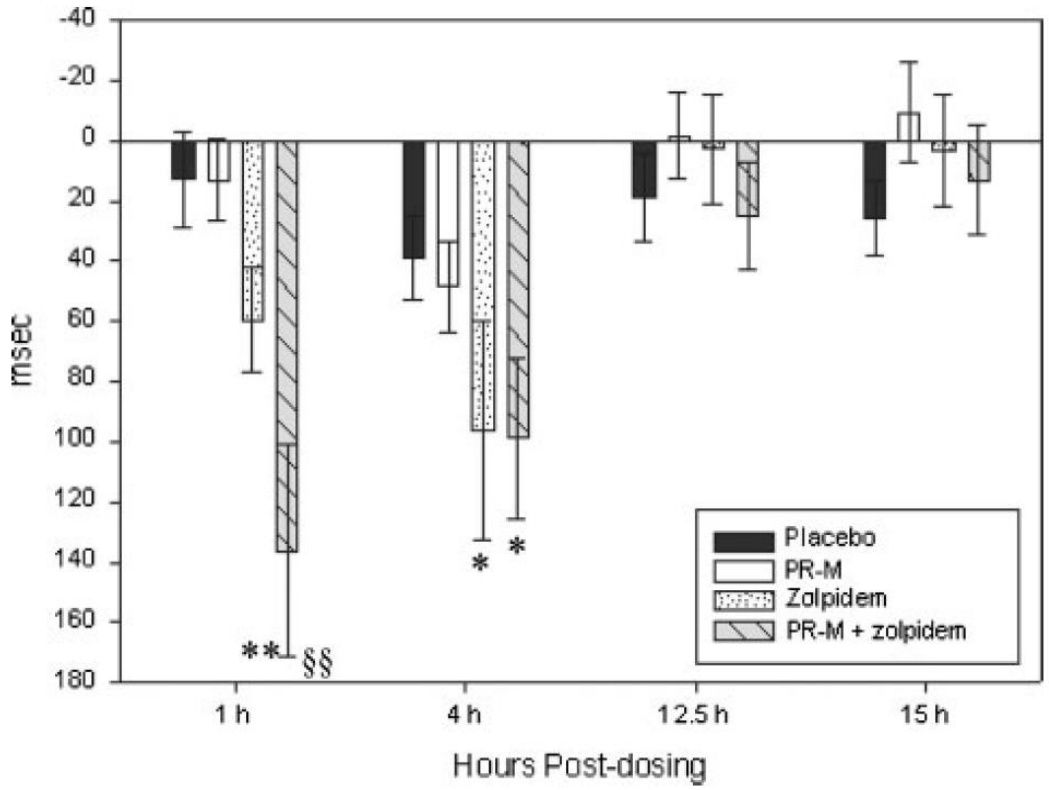


Figure 2. Power of attention factor score in the cognitive tests as a function of the treatment and the hours post-dosing (means ± standard errors; $^{*}p < 0.05$ compared to placebo; $^{\S\S}p < 0.001$ compared to PR-M)

Conclusions of the Study (pages 702-703)

- The third conclusion is that clinicians should be aware that co-dosing PR-M with zolpidem can cause acute sedative effects, greater than those expected with zolpidem alone, and which will have a significant impact on the patient's cognitive abilities.
- However, these effects are short-lived and when considered in use with an insomniac population, the evidence here strongly supports the conclusion that there will be no hangover effects on cognitive function next morning that will impair the ability to conduct the activities of daily living.