

Translational Medicine: The Utility of Cognitive Function Assessments in Phase I Clinical Research Trials

Steven T. Satek, MBA¹, James M. Ferguson, MD^{1,2}, Melissa L. Grohs¹, Keith A. Wesnes, PhD³

¹Cognitive Drug Research, Chicago, IL, ²University of Utah School of Medicine, Salt Lake City, UT, and ³Cognitive Drug Research, Goring-on-Thames, UK

Abstract

Translational medicine study designs and procedures decrease drug development time and expense by using a variety of techniques to disqualify "flawed" new compounds in development early in the research process. At the same time they help to identify the most promising compounds for further development. One of the tools available to translational medicine is the use of cognitive function testing. In phase I cognitive testing can identify compounds with "cognitive toxicity" or unwanted CNS side effects that normally are not evaluated until late in the development process. The information from cognitive function testing can help the drug development team make the critical decision whether or not to invest additional time, money, and resources in support of a compound.

The Cognitive Drug Research (CDR) computerized cognitive assessment system has been used in clinical trials world wide for over 20 years. The test battery has been used in healthy volunteers and symptomatic patients in all phases of drug development.

The utility of automated cognitive assessment in Phase I clinical trials to make go/no-go decisions are seen in numerous clinical trial programs. Positive effects in Phase I have predicted subsequent positive outcome in clinical trials for S-12024 in Alzheimer's disease, GTS-21 in Schizophrenia, TC-1734/AZD3480 in both MCI and AAMI, and NS2359/GSK372475 in ADHD.

In addition, the scopolamine model of dementia has been used in pharmacodynamic trials of anti-dementia drugs successfully predicting the beneficial effects of donepezil and the Huperzine derivative ZT-1. More importantly the scopolamine model identified the lack of an effect of the glycine pro-drug milacemide which was consistent with the lack of positive effect seen in patients with Alzheimer's Disease. Cognitive testing in Phase I indicated a lack of cognitive toxicity for darifenacin, a selective M3 receptor antagonist, in young and elderly normal subjects. These results were consistent with the lack of CNS adverse events seen with this compound in Phase II and III studies.

Cognitive testing in Phase I using appropriately designed, validated test batteries for which normative data is available provides information that is predictive of the outcome of future development. This tool, along with other techniques used in translational medicine can help decrease drug development time and costs.

Introduction

Translational Medicine is a category of medical research whose purpose is to directly connect basic research to patient care. The hypothesis of this presentation is that automated cognitive testing can be effectively employed in early clinical development to support decisions related to the advancement of compounds to advanced phases.

In order for automated cognitive testing to be suitable for inclusion early clinical pharmacology trials, the systems must be brief, repeatable, allow group testing scenarios, not require specialist administration and require non-verbal responses. The proprietary Cognitive Drug Research (CDR) system exceeds those requirements with high sensitivity, validity and reliability.

This poster describes the CDR system and provides case studies of how CDR has been successfully utilized as a translational tool to support compound development decisions.

The CDR Cognitive Assessment System

The CDR computerized assessment system has been designed to provide a valid, reliable and sensitive tool to assess cognitive functions in normal subjects and diseased patient populations. It is the most widely used automated system in clinical research having been used in over 900 clinical trials at 1,000 research sites in 38 countries and 52 languages. The CDR database is the largest in the world and includes data from clinical trials of many classes of drugs, toxins, and environmental factors that affect cognitive functioning. Data from research programs utilizing CDR's system have resulted in



over 200 journal publications and 425 poster abstracts.

The CDR computerized cognitive assessment system was used to collect test data used in the following case studies. All tasks were computer controlled and the responses recorded via a response module with two buttons marked YES and NO. The following tasks comprise CDR's Core Battery.

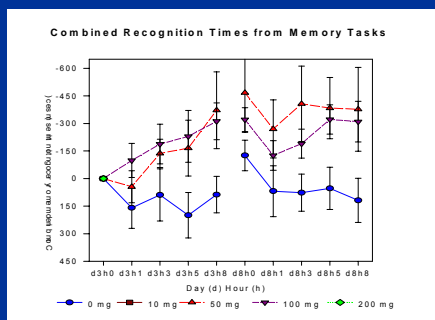
- Immediate Word Recall
- Simple Reaction Time
- Digit Vigilance
- Choice Reaction Time
- Spatial Working Memory
- Numeric Working Memory
- Delayed Word Recall
- Word Recognition
- Picture Recognition
- Bond-Lader Visual Analogue Scales of Mood and Alertness

Case Study 1: S-12024

S12024 is a compound that increases vasopressinergic activity possibly via nicotinic mechanisms. CDR testing was utilized in a multiple-dosing safety and tolerability trial in elderly volunteers and identified a range of cognitive benefits. The results were dose-dependent with the 50 and 100 mg doses most effective. A follow-up bridging study in Alzheimer's Disease patients found enhancements on same CDR tests. A large phase II clinical trial found the 100 mg dose effective in Alzheimer's Disease patients with APOE E4 allele, using MMSE as outcome variable.

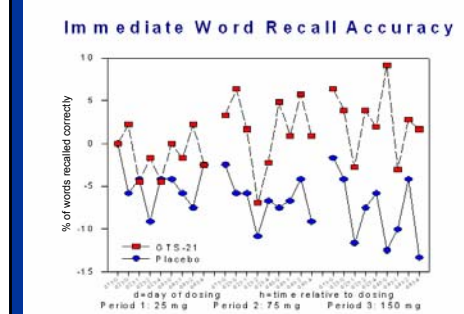
Conclusion: Phase I safety and tolerability trials can be made into proof of concept trials with the simple addition of cognitive testing. Effective doses and dose response curve can be predicted.

References
Wesnes, et al (1994). Pharmacodynamic effects of a repeated oral administration of 4 dose levels of S12024 in 36 elderly volunteers. *Neurobiology of Aging* 15: S100.
Allain, et al (1997). Bridging study of S12024 in 53 in-patients with Alzheimer's disease. *Journal of the American Geriatrics Society* 45: 125-12



Case Study 2: GTS-21

GTS-21 is an oral agonist of the $\alpha 7$ nACh receptor in the CNS that is being studied as a cognitive enhancing therapy. CDR's test battery was added to a multiple ascending dose trial in 18 healthy male volunteers. GTS-21 showed statistically significant enhancement of three measures of cognitive function (attention, working memory, episodic secondary memory) compared to placebo. A relationship between exposure to GTS-21 and the magnitude of the cognitive response was apparent, with maximal effect approached for doses between 75 and 150 mg TID. A follow-up proof-of-concept trial in schizophrenics showed significant neurocognitive improvement on the Repeatable Battery for the Assessment of Neuro-psychological Status total scale score.



Conclusion: The CDR phase one data predicted that GTS-21 may represent a novel treatment for cognitive enhancement. Proof of concept study in schizophrenics verified the prediction.

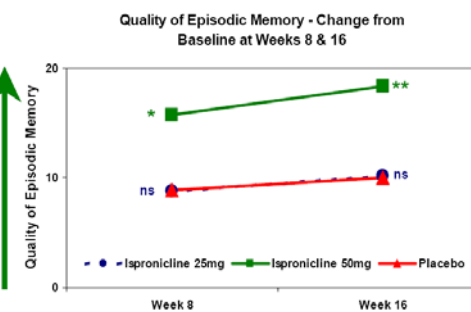
References
Kitagawa et al (1998). Safety, pharmacokinetics, and effects on cognitive function of multiple doses of GTS-21 in healthy male, volunteers. *Neuropsychopharmacology* 28: 542-551.
Olinicy, Freedman et al (2006). Proof-of-Concept Trial of an $\alpha 7$ Nicotinic Agonist in Schizophrenia. *Arch Gen Psychiatry*. 63:630-638

Case Study 3: TC-1734/AZD3480

TC-1734/AZD3480 is a highly selective partial agonist at the $\alpha 4\beta 2$ nAChR. CDR testing was administered in single and multiple dose safety trials. In those trials, cognitive benefits were found on key CDR factor scores including Power of Attention and Quality of Episodic Memory. CDR data supported the decision to advance the compound to proof-of-concept studies in AAMI and MCI populations. Significant positive effects on CDR factor scores found in both populations.

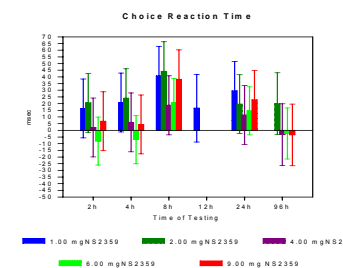
Conclusion: CDR phase one data predicted that TC-1734/AZD3480 may represent a novel treatment for cognitive enhancement. Phase I findings confirmed in proof-of-concept patient trials.

References
Dunbar G (2004) Ispronicline (TC-1734), a Neuronal nicotinic acetylcholine partial receptor agonist that demonstrated excellent safety/ tolerability profile and cognitive enhancement in early studies in humans. American College of Clinical Pharmacology, December 2004, Puerto Rico.
Dunbar G (2007). AZD3480 (TC-1734): Early development in Volunteers and Elderly Subjects Indicating a Beneficial Effect on Cognition 8th International Conference on Alzheimer's and Parkinson's Diseases, 14 - 18 March 2007, Salzburg, Austria



Case Study 4: NS2359/GSK372475

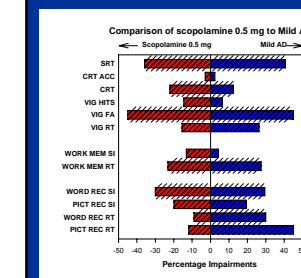
NS2359 is a serotonin, noradrenalin and dopamine reuptake inhibitor. In an early Phase I study utilizing the CDR cognitive assessment system, NS2359 showed an ability to improve attention and memory in healthy volunteers. The development of NS2359 progressed to Phase II trial of adult ADHD which showed positive cognitive effects. Traditional scales failed in this small study.



Conclusion: Cognitive results from phase one effectively predicted results in phase II. The failure of traditional paper and pencil tests in the proof of concept trial demonstrate the utility of sensitive computerized tests in early Phase II studies.

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

Case Study 5: Scopolamine Model of Dementia



Cognitive deficits in Alzheimer's disease and other dementias (e.g. Dementia with Lewy Bodies) acknowledged to be due in large part to damage to central cholinergic functioning. Scopolamine temporarily blocks the activity of cholinergic pathways. It produces cognitive impairments in volunteers which closely resemble Alzheimer's deficits. The CDR system has been utilized in over 25 scopolamine model trials.

In a phase one trial of 10 elderly male and female volunteers receiving four doses of scopolamine 0.5 mg s.c. 2 weeks apart. In counterbalanced order, additionally received placebo, Donepezil 10 mg, or ZT-1 (Huperzine) 1 mg and 1.5 mg. CDR was able to demonstrate both Donepezil and Huperzine's ability to reverse effects of scopolamine on episodic memory and attention domains. A follow-up phase II study of Huperzine demonstrated efficacy in patients with mild-to-moderate Alzheimer's Disease through the ADAS-cog and MMSE assessments.

Conclusion: The use of CDR in the scopolamine model of dementia can predict the efficacy of compounds in patient populations.

References
Zangara A, Wesnes K, et al (2004). The effectiveness of ZT-1 and donepezil in reversing scopolamine-induced cognitive impairment in elderly volunteers. *International Journal of Neuropsychopharmacology* 7 (Suppl): 377

Debiopharm's ZT-1 safe and efficacious in phase I and II trials. *CNS Drug News* #137, 11 May, 2006

FUNDING: Cognitive Drug Research

CORRESPONDENCE: Steve Satek, Cognitive Drug Research, 730 North Franklin Street, Suite 603, Chicago, IL 60660; steves@cognitivedrugresearch.com