

# Clinical research

## *The value of assessing cognitive function in drug development*

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It is difficult to overestimate the need for the definitive evaluation of cognitive function throughout the drug development process. From a safety perspective, patients have the right either to be assured that any new medicine will not disrupt cognitive function, or to an accurate explanation of the likely effects they may expect to experience. Besides safety issues, there is a host of other reasons for wanting such information, not least to measure the efficacy of the numerous cognition enhancers and antidementia drugs under development. It is the responsibility of the developers of medicines to ensure that such data are gathered, and it is the job of regulators to set clear guidelines on how such information is to be obtained, and also to thoroughly scrutinize

*This paper reviews the value and utility of measuring cognitive function in the development of new medicines by reference to the most widely used automated system in clinical research. Evidence is presented from phase 1 to 3 of the nature and quality of the information that can be obtained by applying the Cognitive Drug Research computerized assessment system to ongoing clinical trials. Valuable evidence can be obtained even in the first trial in which a novel compound is administered to man. One application of such testing is to ensure that novel compounds are relatively free from cognition-impairing properties, particularly in relation to competitor products. Another is to ensure that unwanted interactions with alcohol and other medications do not occur, or, if they do, to put them in context. In many patient populations, cognitive dysfunction occurs as a result of the disease process, and newer medicines which can treat the symptoms of the disease without further impairing function can often reveal benefits as the disease-induced cognitive dysfunction is reduced. Another major application is to identify benefits for compounds designed to enhance cognitive function. Such effects can be sought in typical phase 1 trials, or a scopolamine model of the core deficits of Alzheimer's disease can be used to screen potential antidementia drugs. Ultimately, of course, such effects can be demonstrated using properly validated and highly sensitive automated procedures in the target populations. The data presented demonstrate that the concept of independently assessing a variety of cognitive functions is crucial in helping differentiate drugs, types of dementia, and different illnesses. Such information offers a unique insight into how the alterations to various cognitive functions will manifest themselves in everyday behavior. This reveals a major limitation of scales that yield a single score, because such limited information does not permit anything but a quantitative interpretation; and the concept of "more" cognitive function or "less" is manifestly inappropriate for something as complex and diverse as the interplay between cognitive function and human behavior. Finally, the next generations of cognitive testing are described. Testing via the telephone has just been introduced and will have dramatic effects on the logistics of conducting cognitive testing in large patient trials. Testing via the Internet is not far off either, and will come fully into play as the proportion of homes connected to the Internet increases in Europe and North America. There are no sound reasons for not wishing to include cognitive function testing in the development protocol of any novel medicine.*

**Keywords:** Cognitive Drug Research computerized assessment system; computerized cognitive function assessment; attention; working memory; long-term memory

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## Selected abbreviations and acronyms

|             |   |
|-------------|---|
| <b>AD</b>   | <i>Alzheimer's disease</i>                  |
| <b>ADAS</b> | <i>Alzheimer's Disease Assessment Scale</i> |
| <b>CDR</b>  | <i>Cognitive Drug Research [system]</i>     |
| <b>CFF</b>  | <i>critical flicker fusion</i>              |
| <b>CRT</b>  | <i>choice reaction time</i>                 |
| <b>DC</b>   | <i>disturbance of consciousness</i>         |
| <b>DLB</b>  | <i>dementia with Lewy bodies</i>            |
| <b>DSST</b> | <i>Digit Symbol Substitution Test</i>       |
| <b>GABA</b> | <i>gamma-aminobutyric acid</i>              |
| <b>5-HT</b> | <i>5-hydroxytryptamine</i>                  |

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any data presented. However, before any of this is possible, those responsible for assessing cognitive function, ie, psychologists, need to properly define the role of cognitive function in everyday behavior, develop appropriate measures, and also to apply them to clinical trials. The purpose of this paper is to describe the development and application of the most widely used automated cognitive function assessment system in worldwide clinical research, the Cognitive Drug Research (CDR) computerized assessment system.

### The Cognitive Drug Research computerized assessment system (CDR system)

There is a widespread misconception that the description “sedative” or the warning “do not drive or operate dangerous equipment” are in some way adequate to describe either the myriad effects that medicines may have on everyday behavior, or the full risks and consequences of such effects. Together with the widespread use of traditional pencil and paper tests in drug development, plus the assessment of psychophysical thresholds (eg, critical flicker fusion [CFF] frequency), this has led many to believe that simply utilizing such assessments can properly and fully identify the behavioral consequences of drugs. This belief is not shared by all psychologists in this area, particularly those who are interested in applying the principles of cognitive psychopharmacology to clinical trials. The fundamental tenets of cognitive psychopharmacology are:

- That there are major areas of cognitive function (eg, attention, working memory, episodic secondary mem-

ory, the control of movement, etc) which underpin everyday behavior.

- That these can be assessed using tests of cognitive function.
- That these tests need to independently assess these various functions as far as possible.
- That the tests must yield sufficient information such that the interpretation of any change can be made definitively.

The criticism of many traditional tests, for example, the Digit Symbol Substitution Test (DSST), is first that they confound a range of functions and second they are not able to rule out speed–accuracy trade-offs. The consequence of the latter problem is that volunteers are not penalized for trading off accuracy against speed. A change in the accuracy of performance as assessed by a pencil and paper test such as the DSST is not a definitive measure of a change in cognitive function, as it might simply represent a change in the strategy with which the task is performed (in the case of the DSST, there is no way of penalizing performance if the symbols are not precisely copied). Other tasks do not measure cognitive function in the first place; for example, CFF frequency is simply a psychophysical threshold, as is, for instance, auditory acuity, and alterations in the threshold may occur via mechanisms that do not involve cognitive function.

This disillusion with traditional techniques has led many researchers to automate tests known to assess as far as possible specific aspects of cognitive function. The principal motivation for automation was to enable speed of performance to be assessed at the same time as accuracy, in order to identify speed–accuracy trade-offs. Tests were selected on the basis of their ability to reflect activity in particular cognitive domains such as attention or verbal recognition. An advantage of assessing speed that soon became obvious was that it was often more sensitive than accuracy. The CDR system has its roots in the automation of tests in the 1970s<sup>1,2</sup> using the early laboratory minicomputers. The full utility of the system was soon realized in the prototypes, which were installed on the early microcomputers, the most successful being the BBC. In order to facilitate the use of the CDR system worldwide, the system was installed on the IBM PC in the mid-1980s, where it still remains; though it is currently being moved from the DOS to the Windows environment. The system has a

range of core tests which can be supplemented by a wide range of additional procedures. It also has the ability to facilitate the administration of traditional tests. The core tests of the system are described in *Table I*. The keyboard is not used in any test, most involving responses made via a customized response module containing YES and NO buttons. There are over 50 parallel forms of the tests, which are available in most languages and are all brief (1 to 3 minutes; although some tasks can be extended for special requirements). Different versions have been developed and validated for volunteer (young and elderly) and various patient populations.<sup>3,4</sup> Testing can be directly linked to an electroencephalograph (EEG) and evoked potential recording in order for behavioral and electrophysiological effects to be integrated.<sup>5-8</sup> The utility, reliability, and validity of the system have all been exhaustively demonstrated and discussed,<sup>3,9-15</sup> and will be further elucidated together with the widespread data on the sensitivity of the system in the following sections.

|   |
|---|
| <b>ATTENTION</b>  |
| • Simple reaction time  |
| • Choice reaction time  |
| • Digit vigilance   |
| <b>EXECUTIVE FUNCTION AND WORKING MEMORY</b>                    |
| • Rapid visual information processing                           |
| • Semantic reasoning  |
| • Logical reasoning   |
| • Articulatory working memory                                   |
| • Spatial working memory  |
| <b>EPISODIC SECONDARY MEMORY</b>                                |
| • Word recall   |
| • Word recognition  |
| • Picture recognition   |
| • Face recognition  |
| <b>MOTOR CONTROL</b>  |
| • Joystick tracking task  |
| • Tapping task  |
| • Postural stability task                                       |
| <b>PSYCHOPHYSICAL THRESHOLDS</b>                                |
| • Critical flicker fusion (with and without pupil size control) |

**Table I.** The tests available in the CDR system.

## Screening for unwanted cognitive toxicity

Historically, most types of central nervous system (CNS) drugs, and many others (eg, antihistamines), produced impairments in human cognitive function that compromise the ability of patients to undertake the activities of daily living. Clearly, in populations where cognitive function is already compromised, eg, elderly, demented, or schizophrenic patients, such effects can pose very serious problems. One potential advantage of many newer medicines under development is that they are relatively free of such unwanted effects. Such effects (or confirmation of their absence) can be sought in the early stages of drug development, and the use of the CDR system in such research will be described for a variety of types of compound. Another possible problem is new medicines interacting with other medications or alcohol, and work in this field will also be covered.

### Phase 1 single and multiple safety and tolerability trials

Cognitive function testing can be conducted in any phase 1 trial, even first-time-to-man trials.<sup>16-18</sup> The selection of tests in the latter type of trial should generally be restricted to core tasks, the battery lasting roughly 15 to 20 minutes. There are several advantages of incorporating cognitive testing into first-time-to-man trials. One is that the range of doses studied is almost invariably the widest that will be administered in the development program, and thus it is an ideal opportunity to establish the pharmacodynamic relationship to this dose range. If no effects are identified even at very high doses, this is a fair prediction that none will be encountered with single doses in the rest of the development program. Further, if the drug shows tolerability problems or poor pharmacokinetics, and development is stopped, any information about the cognitive effects (or lack of them) will help decide whether it is worth bringing forth similar candidates with slightly different molecular structures. Finally, if dramatic impairments are noted in a compound hoped to be free from such effects, then development can be stopped at this point.

ME3127, a novel anxiolytic, is close to a full agonist at some subtypes and a partial agonist at other subtypes of gamma-aminobutyric acid-A (GABA<sub>A</sub>) receptors. ME3127 was studied in a first-time-to-man, double-

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blind, placebo-controlled, escalating single-oral-dose study.<sup>16</sup> Fifty-six healthy young volunteers in 7 groups of 6 volunteers received single doses of ME3127 (1, 2, 4, 8, 16, 32, or 64 mg) and 2 further volunteers in each group received placebo. The cognitive assessments were completed predose, and at 2, 4, 8, and 24 hours postdose. A dose-dependent range of impairments was detected, the highest dose having clearly identifiable effects on a range of measures. In a follow-up study,<sup>19</sup> each of the 3 groups of 6 volunteers received multiple doses of ME3127 (8, 16, or 32 mg) and 2 volunteers in each group received placebo. Testing was performed on day 1 and day 9. On day 1, a wide range of effects was identified, as seen in the previous trial. Importantly, these effects faded with repeat dosing and relatively few negative effects were seen on day 9—in fact, on working secondary memory tasks some improvements were seen. NS2389 acts by blocking the neuronal uptake of 5-hydroxytryptamine (5-HT) as well as other monoamines such as noradrenaline and dopamine.<sup>18</sup> The CDR system was used to study the compound in single doses of 1, 2, 4, 8, 16, 32, 48, and 72 mg in a double-blind, placebo-controlled study in 64 healthy male volunteers. Some evidence of impairment was detected at various doses in this study.

A selective M<sub>3</sub> muscarinic receptor antagonist (UK 76,654) developed for the treatment of irritable bowel syndrome was studied in a parallel-group, rising-dose, placebo-controlled, single and 9-day multiple-dosing study.<sup>17</sup> One of the advantages of this selectivity for the M<sub>3</sub> receptor is that it should be relatively free from the unwanted cognitive impairment seen with existing non-specific anticholinergic treatments. The CDR system was administered six times a day in the single-dose stage and on the first and last day of the multiple-dosing period. No cognitive impairment was seen up to 20 mg, while at the next dose, 40 mg, some impairments were seen. This study gave the developers valuable information about the dose range over which no cognitive impairment would be seen in patients.

## Phase 1 trials with internal controls

Another common procedure in phase 1 trials is to include an internal control known to impair function, against which the novel compound can be directly compared.

Umespirone, a novel compound with D<sub>2</sub> antagonist and 5-HT<sub>1A</sub> agonist properties was compared with buspirone

30 mg using the CDR system in young volunteers.<sup>20</sup> The pattern and time course of the cognitive effects of the two compounds were different, peak effects of buspirone were seen shortly after dosing and fading thereafter, whereas the effects of umespirone persisted for up to 23 h. Although both drugs objectively impaired attention, buspirone reduced self-rated alertness, while umespirone increased self-rated alertness and showed a potential to improve secondary verbal memory. Abecarnil, a  $\beta$ -carboline, and lorazepam were compared in a single-dose trial.<sup>21</sup> Abecarnil was found to produce a comparable impairment to that produced by lorazepam. In another trial in young volunteers, single doses of amitriptyline 75 mg, hydroxyzine 25 mg, and lorazepam 1 mg were shown to have quite different profiles of cognitive impairment.<sup>8</sup> The most striking difference was the much greater attentional impairment produced by amitriptyline in comparison to the greater decrements to the speed of memory processes produced by lorazepam. Such double dissociations illustrate the value of assessing different domains of cognitive function when attempting to differentiate compounds.<sup>13</sup> In another trial, 18 healthy male volunteers took part in a 6-way crossover trial to contrast DU 29894 (3 and 10 mg), a novel D<sub>2</sub> antagonist/5-HT<sub>1A</sub> agonist, with sulpiride 400 mg, haloperidol 3 mg, and flesinoxan, a novel selective 5-HT<sub>1A</sub> agonist.<sup>22</sup> All the compounds produced impairments, though the time course, magnitudes, and cognitive profiles of effects were different. Importantly, on some measures, each compound could be differentiated not only from placebo but also from the others. Mazapertine, a selective D<sub>2</sub> and D<sub>3</sub> antagonist and also an adrenergic and 5-HT<sub>1A</sub> antagonist, was found to be relatively free from cognition-impairing activity, though the parallel-group design employed was less powerful than that of the previous trial.<sup>23,24</sup>

The acute CNS effects of the  $\beta$ -adrenergic blocker atenolol 100 mg and the angiotensin-converting enzyme (ACE) inhibitor cilazapril 5 mg were contrasted in volunteers using the CDR system.<sup>25</sup> Self-ratings of alertness were found to decline for both compounds yet no cognitive effects were seen from the CDR tests for either compound. This illustrates that volunteers can experience reductions in alertness in the absence of objective evidence of decreased mental efficiency. In another trial, exactly the opposite occurred. A group of 14 elderly volunteers were dosed for 4 days with haloperidol 3 mg, olanzapine 3 mg, or placebo in a

3-way crossover design.<sup>26</sup> The CDR system identified clear and widespread impairment with olanzapine 3 mg on the first day of dosing, which was still present, though significantly reduced on several measures, by 4 days and had completely passed after 48 hours of washout. In contrast, haloperidol showed a smaller overall impairment on the first day, which had increased dramatically by the fourth day and was still marked on many measures after 48 hours of washout. This study predicted a clear difference between the two compounds in cognitive toxicity with repeated dosing in patients, which has been largely borne out by subsequent clinical trials. Interestingly, despite being markedly impaired with haloperidol after 48 hours of washout, the volunteers reported no lowering of self-rated alertness compared with predosing, which is the opposite pattern to that described in the previous trial. Despite this clear impairment with haloperidol 3 mg in the elderly, another trial in this population, which used a 2-mg dose in an attempt to avoid this extreme cognitive toxicity, found relatively little overall impairment.<sup>27</sup> On two measures, haloperidol 2 mg was shown to be inferior to amisulpride 50 and 200 mg, the latter drug showing no impairment and some occasional signs of enhancement. In another trial in elderly volunteers, acute doses of moclobemide 100 and 300 mg were shown to produce little overall impairment and some enhancement of memory processes compared with trazodone 150 mg, which produced widespread and marked impairment.<sup>28</sup>

Remacemide, a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist under development for the treatment of epilepsy, was found to lead to dose-dependent cognitive impairment in acute doses up to 400 mg in a 5-way, placebo-controlled, crossover design in 16 young volunteers.<sup>29</sup> Diazepam 10 mg was used as an internal control, and produced a similar range of impairments as remacemide 400 mg, though the profile of these impairments in terms of the magnitudes of actions on various aspects of function was quite distinct. However, in subsequent repeated dosing trials, no effects of remacemide have been discovered, despite the doses being equivalent to therapeutically relevant equivalents in enzyme-activated patients.<sup>30</sup> This suggests that, for some compounds, such as olanzapine mentioned previously, tachyphylaxis for cognitive impairment can occur with repeated dosing.

The benzodiazepine antagonist flumazenil has been shown to reverse the effects of midazolam on cognitive

function in healthy volunteers.<sup>31</sup> Interestingly, despite this effect, when given alone in three infusions of 0.5, 2.5, and 5 mg, flumazenil produced a wide range of cognitive impairment in a placebo-controlled, double-blind, crossover trial.<sup>32</sup> Similar effects when flumazenil is administered to patients with Alzheimer's disease (AD) will be reported in a later section.<sup>33</sup>

There is obvious interest in the cognitive effects of the opioids when used to treat cancer pain. Acute oral doses of the weak opioid dextropropoxyphene napsylate (100 and 200 mg) were contrasted to lorazepam 2 mg in a double-blind, placebo-controlled, 4-way, crossover design in young volunteers.<sup>34</sup> Lorazepam 2 mg produced a wide range of cognitive impairments in all attentional and working and secondary memory tasks employed, as well as self-rated alertness. Lorazepam in addition produced a significant reduction in the frequency of fusion in the CFF task. In contrast, the only effect seen with dextropropoxyphene was a reduction in the frequency at which fusion took place in the CFF task with the 200-mg dose, which was directly comparable to the effect of lorazepam on this measure. This is a clear demonstration of how misleading CFF data might be in the absence of data from cognitive tasks. Had the only data for this study been from the CFF procedure, it might have been falsely concluded that dextropropoxyphene 200 mg has the same cognition-impairing potential as lorazepam 2 mg, whereas, as can be seen, nothing could be further from the truth. A companion trial using the same design compared acute oral doses of morphine 10 and 15 mg with lorazepam 1 mg and placebo.<sup>35</sup> Lorazepam again influenced all tasks, though the effects were smaller in magnitude than the large dose in the previous study. Interestingly, self-rated scores of alertness did not show a significant effect, illustrating the greater sensitivity of objective tests of cognitive function. Morphine influenced CFF in a similar fashion and to a similar degree to dextropropoxyphene in the previous study. The other effect of morphine was to disrupt episodic secondary memory, both the ability to correctly recall words and to correctly recognize pictures being disrupted. In the third study in this series,<sup>36</sup> repeated dosing of dextropropoxyphene napsylate 100 mg, morphine 10 mg, lorazepam 0.5 mg, and placebo were contrasted in a double-blind, 4-way, crossover design in young volunteers. The volunteers received the four doses of each treatment administered at 4-hourly intervals over a 36-hour testing period, testing being conducted prior to dosing, and after 4, 8, 12, 16,

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26, 30, and 36 hours. Lorazepam affected the speed components of all tasks employed, except that of the digit vigilance task. Dextropropoxyphene disrupted choice reaction time and lowered the ability to correctly recognize pictures. Morphine had some effects, including a lowering of the frequency of fusion in the CFF task. Another study has evaluated the effects of intravenous morphine on the performance of young volunteers.<sup>37</sup> Here the intention was to identify a dose of morphine that could reliably induce a cognitive deficit in a 12-year-old volunteer, crossover design in order that it might be used as an internal standard in future evaluations of novel opioid compounds. Three doses of morphine (2.5, 5, and 10 mg per 70 kg, infused over 15 minutes) were contrasted to placebo in a double-blind study. Few, if any, effects were found with the two lower doses, whereas the 10 mg/70 kg infusion slowed speed on all tasks, disrupted picture recognition and tracking, and lowered self-rated alertness.

## The identification of residual impairment

Another unwanted effect is for hypnotics taken in the evening to facilitate sleep to have residual effects the next morning, ie, for the “sedative” effects to persist such that the individual is less capable of performing the tasks of daily living. In normal volunteers, temazepam 40 mg was compared with flurazepam 30 mg in a double-blind, placebo-controlled, crossover design.<sup>38</sup> Next morning, volunteers were impaired on the rapid visual information processing task if they had taken flurazepam the night before rather than placebo or temazepam. There were no effects detected on two traditional measures, DSST and CFF. Interestingly, although none of the volunteers typically experienced sleep difficulties, both hypnotics produced significant improvements in a range of aspects of self-rated sleep quality. Flurazepam produced greater benefits on sleep quality, at the cost of residual effects on performance. In a follow-up trial using the same general design, temazepam 10 and 20 mg were both found to improve sleep quality without having residual effects on performance.<sup>39</sup> Finally, in a third trial, volunteers were kept awake all night to simulate shift-work and were administered temazepam 20 mg the morning after to facilitate daytime sleeping.<sup>39</sup> The trial identified that the volunteers slept better with temazepam than with placebo, and again that temazepam had no residual effects on performance.

## Interaction trials

Such trials are important and are generally conducted in volunteers, though there is no scientific reason why they could not be conducted in patient populations. The major reason for conducting them in volunteers is the ease of recruitment of the subjects and the avoidance of the complication of concomitant medications.

Alcohol interaction trials are the most common, as all compounds carry the risk that the patient might consume alcohol while taking the medication. Research has established that the “everyday” perception of the effects of alcohol do appropriately describe the actions of alcohol. At very low doses, there is the possibility that performance is enhanced.<sup>40</sup> However, above 2 units, attention is impaired, anterograde amnesia is produced, skilled coordination is disrupted, postural stability is decreased, and self-ratings of alertness and clear-headedness decline.<sup>41</sup> These are the aspects of cognitive function which underpin the everyday behavioral effects of alcohol. To properly conduct an alcohol interaction trial of the effects upon cognitive function, the following conditions must be satisfied:

- The dose of alcohol must be relevant. A typical dose range is 0.5 to 0.7 g/kg, which puts individuals around the legal limits for driving in Europe.
- The timing of administration of alcohol and the study compound must be arranged such that their peak concentrations coincide.
- Cognitive testing needs to be conducted prior to dosing and at various times after. The aim here is to identify firstly whether at the time of peak absorption any increase in the cognitive effects is identified, and secondly whether the persistence of any effects is affected.
- The tests employed need to be sensitive to the effects of the dose of alcohol administered and also relevant to the known behavioral effects of alcohol (eg, to include tests of attention, memory, coordination, and postural stability).
- Tests not typically sensitive to alcohol should be included to identify whether the interaction would increase the range of cognitive functions affected by alcohol.

Another common mistake is to allow statisticians to design the trial as if it were a pivotal phase 3 study. It is perfectly appropriate to have more than one outcome measure in such trials, and the problem of multiplicity is actually reversed. To select one primary variable, for

example, attention, and to relegate factors such as coordination, memory, and postural stability to the level of secondary outcome variables makes no sense in terms of the everyday importance of the functions that these tests assess. Alcohol has multiple actions on cognitive function, and the trial must be designed to measure the likelihood of interaction on these multiple actions. The aim is to provide reassurance that the compound under evaluation does not interact to produce effects that we would not expect to see. The strength of such trials thus lies in their demonstration that, despite measuring a range of functions, there is little or no evidence that interactions exist. Trials that have a single primary variable face the criticism that they are not properly addressing the full potential of the compound to interact with alcohol, and thus the remit of the conclusions based on the trials should be restricted to the function(s) assessed as the primary variable(s).

There are two basic design types in most interaction trials. The most simple is the classic 2×2 factorial crossover design generally involving acute administration of the study compound. In such a design the four combination possibilities are covered:

- Placebo alcohol and placebo study compound.
- Placebo alcohol and active study compound.
- Active alcohol and placebo study compound.
- Active alcohol and active study compound.

The major alternative design involves multiple dosing with the study compound. Here, two multiple-dosing periods take place, one with the active study compound and the other with the placebo study compound. After a sufficient time for the study compound to reach steady state, 2 test days, separated by 2 or 3 days, occur on which active alcohol and placebo alcohol are administered, in counterbalanced order between volunteers. The two dosing periods are either crossed-over with an adequate washout interval or a split-plot design is used. The latter is generally the case if the dosing period is 14 days or more. The efficiency of the crossover design here stands comparison with the 2×2 factorial, which is impressive considering the requirement of repeated dosing.

The smallest sample size in such trials is 12,<sup>42</sup> and in some studies as many as 30 volunteers are tested.<sup>43</sup> The following trials all used the classic 2×2 factorial design, and found clear effects of alcohol but no potential of the study compounds to produce interactions. Four used young volunteers, no interaction being found for

the antiepileptic tiagabine,<sup>42</sup> the NMDA antagonist remacemide,<sup>43</sup> the antiobesity compound sibutramine,<sup>44</sup> lorazepam, or the β-carboline abecarnil.<sup>21</sup> In a trial with elderly volunteers, no interactions were detected for the muscarinic agonist SB-202026.<sup>45</sup> The multiple-dosing design was employed in a crossover study to evaluate the interaction potential of alcohol and the selective serotonin reuptake inhibitor (SSRI) fluvoxamine in young volunteers.<sup>46</sup> No signs of an interaction were identified in this trial. In an unusual design, the effects of two doses of moclobemide (100 and 300 mg), trazodone 150 mg, and placebo were evaluated in elderly volunteers.<sup>28,47</sup> Twelve of the volunteers had the four dose conditions in a crossover design, on each occasion receiving a placebo alcohol dose. Twelve further volunteers had the same four study compound conditions, but also received alcohol 0.5 g/kg on each occasion. No interactions with alcohol were identified for either compound.

Drug–drug interaction trials follow the same basic design as alcohol interaction trials and the same basic design rules generally apply, with the added complication that in some trials it is desirable for both drugs to reach steady state. In a series of trials looking for interactions with the SSRI sertraline, parallel-group designs were employed. In one trial, phenytoin was administered to all volunteers for 24 days.<sup>48</sup> From day 8 onwards, sertraline was administered to half the volunteers and placebo sertraline to the other half. Cognitive testing was performed prior to dosing and repeatedly postdosing on days 0, 7, and 24. There was no evidence that phenytoin alone impaired performance or that when dosed with sertraline any cognitive effects appeared. In a second trial, carbamazepine was administered to all volunteers for 32 days.<sup>49</sup> From day 16 onwards, sertraline was administered to half of the volunteers and placebo sertraline to the other half. Cognitive testing with the CDR system was performed repeatedly on days 1, 15, and 32. Carbamazepine impaired attentional efficiency, slowing performance on simple reaction time, choice reaction time, and digit vigilance. These effects were still evident after 32 days of dosing. There was no evidence that sertraline had an influence on this disruption to attention, nor did any other effects emerge when sertraline was codosed with carbamazepine. In a third study,<sup>50</sup> placebo was given on day 1, and a single dose of haloperidol 2 mg was administered to 24 healthy young volunteers on day 2 and again on day 25 of the study period. Sertraline

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was administered from day 9 onwards to 12 volunteers, the other 12 receiving placebo sertraline. The CDR system was administered repeatedly on days 1, 2, and 25. Haloperidol produced impairments in attention on day 2 of the study, yet amazingly, with no intervening dosing, the second single dose administered 23 days later produced greater impairment. On measures affected the first time, the effects started sooner and were of greater magnitude, while functions not affected on day 2 were impaired on day 25. Of 20 measures, 10 were impaired to a significantly greater extent on day 25 than day 2. This effect reflected a phenomenon seen in animals dosed with haloperidol termed “time-dependent sensitization” and was the first demonstration that such a phenomenon exists in man. In other drug–drug interaction work, no evidence was obtained for an interaction between the SSRI fluoxetine and the 5-HT<sub>1A</sub> agonist flesinoxan.<sup>51</sup>

In the 11 studies described above, no interactions were seen. The same was true of the first of two interaction trials conducted with the novel antihypertensive moxonidine.<sup>52</sup> In the first trial, no interaction between moxonidine and the antidepressant moclobemide 300 mg was identified. However, in the second study, a clear interaction between moxonidine and lorazepam 1 mg was identified. In this trial, lorazepam 1 mg produced the profile of impairment characteristic of this type of benzodiazepine. Moxonidine 0.4 mg dosed alone produced no effects, but when the two drugs were codosed, the impairment identified was significantly greater than that of lorazepam 1 mg. This interaction was seen for the following CDR measures: speed of detections in the digit vigilance task, simple reaction time, choice reaction time, and visual tracking. These were clear interactions, which would disrupt the attentional capacity of patients taking lorazepam 1 mg and moxonidine 0.4 mg together. Historical data, however,<sup>34</sup> showed that the impairments with the combination were no greater than what would be produced by lorazepam 2 mg, which will give clinicians a frame of reference when advising patients of the likely consequence of taking the two medications together.

## Screening for desired cognitive effects

Here the purpose of cognitive testing is to identify desired cognitive effects, which are for the most part either reversals of existing deficits or improvements to

normal functioning. Over the last 20 years, there has been a massive investment in research into agents to treat dementia, particularly AD. This has in turn led to interest in treating a range of conditions in which cognitive function is impaired, not least normal aging. The implicit assumption of many researchers in this field is that impairments in function are potentially capable of being reversed, but that normal function cannot be improved.<sup>53</sup> This assumption is fallacious, as will be illustrated in the next section.

## Cognition enhancement

A program of research was initiated at Reading University in the early 1970s into the effects of nicotine on human attention. The basis for the research was the known effects of nicotine on the neurotransmitter acetylcholine, and the aim of the research was to provide evidence at the human level that nicotine, by enhancing cholinergic function, would improve human attention.<sup>1,2</sup> The research showed that nicotine administered via smoking was capable of improving performance on visual and auditory vigilance tasks,<sup>1</sup> the rapid visual information processing task,<sup>54,55</sup> and the digit vigilance task.<sup>56</sup> Further research showed that improvements on the rapid visual information processing task could be seen puff by puff,<sup>57</sup> that higher-nicotine-yield cigarettes improve performance more than lower ones,<sup>54,58</sup> that the ability to detect the targets was improved together with the speed with which the targets were detected, and that the latency of the evoked potential to the targets was shortened by the same amount as the latency of the response was reduced.<sup>5</sup> A review of 12 years of this research illustrated the robustness of these findings: “Every nicotine-containing cigarette we have studied improves performance. Improvements occur irrespective of the duration of testing, the speed of presentation of the digits, the density of targets, whether or not subjects smoke while performing, whether or not they are filmed, whether or not electrocortical activity is measured in another laboratory, and whether testing is carried out in the morning or afternoon.”<sup>59</sup> This work has provided valuable information on the pharmacological basis of the smoking habit.<sup>60</sup> As the research was conducted in healthy young volunteers, it demonstrated that enhancements to cognitive function can be detected in this population. As convincing as the findings were, it was still necessary to



prove beyond reasonable doubt that they were due to nicotine. Thus, nicotine was administered in tablet form in various studies. These tablets were found to improve performance on the vigilance task<sup>61</sup> and on the rapid visual information processing task.<sup>62</sup> Importantly, the improvements in vigilance occurred in smokers and nonsmokers, and on the rapid visual information processing task nicotine tablets improved the speed and accuracy of nonsmokers. This work has been widely replicated in other laboratories (for reviews, see references 58 and 63). Of particular interest are improvements in rapid information processing seen with nicotine gum<sup>64-66</sup> and with a nicotine inhaler.<sup>67</sup> This body of work identified that improvements in normal cognitive function could be produced by pharmacological agents, and showed that computerized tasks were particularly suitable for identifying such improvements, notably those in accuracy and speed. It also helped establish the role of the cholinergic system in human attention. Caffeine has long been believed to enhance mental alertness, and a large body of literature has found data consistent with this; though the effects identified by the CDR system have not been marked or widespread.<sup>68-70</sup> Similarly, some limited effects have been seen with glucose drinks, but again these effects are not robust.<sup>71,72</sup> A more recent series of trials have identified oxygen as a cognition enhancer. Here, short (30 seconds to 3 minutes) administrations of pure oxygen have been shown to enhance performance on a wide range of tasks from the CDR system in healthy young<sup>73-80</sup> and elderly<sup>81,82</sup> volunteers. This wide-ranging work has shown that attention and working and episodic working memory can be enhanced by oxygen in normal volunteers, and again supports the concept that enhancements can be made to nonimpaired cognitive function. Considering the work described above, it is not surprising that potential cognition enhancers are screened in phase 1 trials with young volunteers. NS2330, a compound that combines the inhibition of neuronal monoamine (noradrenaline, dopamine, and serotonin) reuptake with stimulation of the cholinergic system in the prefrontal cortex and hippocampus, was studied in a first-time-to-man safety and tolerability trial.<sup>83</sup> At 1- and 2-mg doses, the compound produced a wide range of enhancements on CDR assessments, including improvements in attention, working memory, and episodic memory, as well as increasing self-rated alertness. These effects were obtained despite the fact that only 6 vol-

unteers received each active dose and 4 received placebo. The effects seemed particularly long-lasting, and, in a follow-up trial,<sup>84</sup> higher doses were studied and effects were assessed up to 360 hours following a single dose. Benefits were seen which were of the same profile as those seen in the previous study and, remarkably, some benefits were seen at 360 hours. In another first-time-to-man trial, a range of doses of NS2359, a noradrenaline, dopamine, and serotonin reuptake inhibitor, was studied in 56 volunteers.<sup>85</sup> The compound showed clear cognition-enhancing properties, particularly with regard to attention and episodic memory. These trials indicate that important evidence on the potential of compounds to enhance cognitive function can be obtained simply by including cognitive testing in safety and tolerability trials, which need to be conducted as part of the drug development process. Further evidence of the utility of this approach comes from a multiple-dosing safety and pharmacokinetic trial in which CDR testing was introduced to evaluate the potential CNS actions of GTS-21, a selective agonist at the  $\alpha 7$  nicotine receptor.<sup>86</sup> Here, despite having only 12 volunteers on active medication and 4 on placebo, a clear profile of enhancements was seen for attention and working and secondary memory. This profile was unexpected, as the effects of nicotine are primarily limited to attention and information processing and no consistent effects have been seen in the world literature of beneficial effects of nicotine on memory.<sup>58,63</sup> This indicates that the selectivity of the compound to the  $\alpha 7$  subtype of the receptor is a particularly promising avenue for cognition enhancement. Finally, in a crossover study with 12 young volunteers, the anticholinesterase physostigmine was found to produce a range of enhancements of attention and episodic memory.<sup>87</sup> This is one of the few published demonstrations of an anticholinesterase improving function in unimpaired volunteers.

Many researchers feel that the elderly are better targets for cognition enhancers due to age-based cognitive decline. Certainly the CDR system is highly sensitive to such declines (see, for example, reference 88), though generally there is little systematic evidence that the elderly respond more readily to cognition enhancers than the young.<sup>81,82</sup> S-12024, a pronoradrenergic compound was found to improve cognitive function in a multiple dose safety and tolerability trial.<sup>89</sup> Interestingly, here the improvements occurred in aspects of function which had declined when the population was

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compared with younger volunteers. HOE 427, an ACTH<sub>4-9</sub> analogue (ACTH: adrenocorticotrophic hormone), was found to produce some evidence of improvement in a 4-way, crossover design in 20 elderly volunteers.<sup>90</sup>

Serendipity can also play a part in drug development. The CDR system was included in trials of flesinoxan, a 5-HT<sub>1A</sub> agonist, in order to ensure the compound was relatively free from cognition-impairing potential. Unexpectedly, cognition enhancement was seen, and, in a follow-up study, these effects were confirmed in young and elderly volunteers, though the effects were greatest for the eldest volunteers, providing evidence relevant to the debate referred to in the previous paragraph.<sup>91</sup> Further, in four of the interaction trials, beneficial effects of the study compounds were seen. This occurred for moclobemide in both elderly<sup>47,92</sup> and young volunteers,<sup>52</sup> and also for sibutramine<sup>44</sup> and SB-202026.<sup>45</sup>

## Scopolamine model of dementia

Another part of the research program initiated at Reading University that was mentioned at the beginning of the previous section was to identify the cognitive effects of the muscarinic cholinergic antagonist scopolamine. Here, the cholinergic system was further implicated in the control of human attention by trials that showed that cholinergic blockade disrupted attention on the vigilance task<sup>93</sup> and also on the rapid visual information processing task.<sup>62</sup> Subsequent research extended the range and scope of such findings, showing that all measures of the CDR system were sensitive to the effects of cholinergic blockade.<sup>94-99</sup> Further work has identified the relationship between the behavioral deficits induced by cholinergic blockade and the pharmacokinetics of scopolamine,<sup>100</sup> EEG changes,<sup>94</sup> positron emission tomography (PET) changes,<sup>101</sup> future cognitive decline in the elderly,<sup>102,103</sup> and the cognitive deficits seen in AD.<sup>104-107</sup>

The growing recognition that cholinergic deterioration underpinned the cognitive deficits in AD, plus the response of AD patients to anticholinesterases and the known cognitive effects of cholinergic blockade with scopolamine in volunteers, led to the idea that scopolamine could produce a model of some of the core cognitive deficits in AD. This idea was further developed when nicotine was found to reverse the effects of scopolamine on attention in young volunteers.<sup>108</sup>

The opportunity has thus existed for over 16 years to utilize a model to help screen potential anti-Alzheimer drugs in phase 1. The validity of this model has been widely established<sup>109-112</sup> and a wide variety of drugs have been screened.

The model is particularly sensitive to anticholinesterases, for example, physostigmine 2 mg subcutaneously has been found to rapidly and completely reverse the impairment produced by scopolamine on all CDR tasks employed, yet these effects were only temporary and had faded an hour later.<sup>113</sup> This mimics the clinical situation perfectly, many early trials showing brief improvements in AD patients during infusions of physostigmine, which faded rapidly on cessation of the infusion. A further trial has confirmed this rapid but temporary action of physostigmine and has further shown it to be strongly dose-dependent.<sup>114</sup> In a further series of studies, velnacrine, an analogue of the anticholinesterase tacrine, was found to produce widespread reversal of the cognitive impairment on CDR tasks produced by scopolamine.<sup>113,115,116</sup> The drug was then administered to AD patients and improvements were seen on some of the CDR tasks that reversals had been identified in the scopolamine model.<sup>115,116</sup> The model is sensitive to a range of compounds, even those without known cholinergic effects. The classic nootropics aniracetam and piracetam have shown activity in the model,<sup>117</sup> as has tenilsetam,<sup>118</sup> though 3OH-aniracetam (Ro 15-5986) showed no activity.<sup>47,119</sup> The monoamine oxidase inhibitor moclobemide has been shown to reverse the effects of scopolamine,<sup>47,119</sup> as has the partial agonist at the strychnine-insensitive glycine site on the NMDA receptor, D-cycloserine, in both young and elderly volunteers.<sup>120,121</sup> The effects of the latter compound were particularly interesting as they were limited to the working and episodic memory effects of scopolamine. FK960 has shown a widespread ability to reverse the effects of scopolamine.<sup>122</sup> Quite a number of compounds have not shown sensitivity in the model, despite performing very well in various animal models, but these have not been released into the public domain. One compound that failed to have any effect on the impairment due to scopolamine was candoxatril, a prodrug of the atriopeptidase inhibitor, candoxatrilat, which increases circulating levels of the peptide hormone atrial natriuretic peptide and inhibits the degradation of endogenous enkephalins.<sup>123</sup>

## Alzheimer's disease

Computerized testing with demented patients is perfectly feasible provided the tests are appropriately designed, short in duration, and easy to explain and follow, the material is clearly visible, the responses are simple to make, and the negative feedback kept to a minimum. The mid-1980s saw the development of the first CDR prototypes,<sup>4</sup> and the CDR system currently used for demented patients has now been widely validated.<sup>3,124</sup> The methodology has now been widely disseminated,<sup>125</sup> and the system has been used to identify the full impairments in attention which accompany the widely recognized memory deficits in AD.<sup>105-107,126</sup> These attentional impairments have been shown to be a result of cholinergic dysfunction<sup>104,106,107</sup> and thus to be legitimate targets for anti-Alzheimer drugs.<sup>104,127</sup> The system has been shown to be particularly sensitive for differentiating different types of dementia from AD, for example, Huntington's disease.<sup>128</sup> It has been contrasted favorably with a wide range of traditional measures in dementia including the Mini-Mental State Examination,<sup>3,128</sup> the Alzheimer's Disease Assessment Scale (ADAS),<sup>128</sup> the Mattis Dementia Rating Scale,<sup>128</sup> the Wechsler Memory Scale,<sup>128</sup> the Cambridge Cognitive Examination (CAMCOG),<sup>129</sup> the Kendrick Battery,<sup>3</sup> the Kew Test of memory, aphasia, and parietal function,<sup>3</sup> and the Stockton Rating Scale.<sup>3</sup> In trials where the sensitivity and discriminability of the CDR system in AD and other types of dementia have been directly compared with various traditional assessments and the ADAS, the CDR system has been found to show higher discriminability than the other techniques, and also to be more sensitive in identifying AD patients than traditional measures as well as the ADAS.<sup>128</sup> Such work has led the International Working Group on Dementia Drug Guidelines to recommend that future AD trials incorporate assessments of attention (currently not assessed by the cognitive subscale of the ADAS), and that computerized systems should be used alongside traditional techniques wherever possible.<sup>130</sup>

The CDR system has been used in various therapeutic trials. The CDR system was the primary outcome variable in a large Food and Drug Administration (FDA)-approved multicenter trial of D-cycloserine in AD.<sup>131,132</sup> Sadly, the compound showed no signs of efficacy, despite showing promise in single doses in animal work and the scopolamine model.<sup>120,121</sup> However, in sub-

sequent publications, the beneficial effects seen in single doses in animal work disappeared with repeated testing, suggesting that this tachyphylaxis might have also occurred in the AD study.<sup>131</sup> S-12024 was tested in a 4-week acceptability and clinical activity trial of S-12024 in 53 inpatients with moderate-to-severe AD, but no clear signs of positive effects were identified.<sup>133</sup> Various anticholinesterases have been shown to be effective in improving both attentional and memory function, including tacrine,<sup>134</sup> velnacrine,<sup>115,135</sup> and galanthamine.<sup>134,136</sup> Importantly, the effects on attentional function are large; the improvements with galanthamine can, for example, take patients 40% back toward scoring normally for their age.<sup>136</sup>

The work with velnacrine indicates that improvements can occur rapidly with anticholinesterases,<sup>115,135</sup> and early phase 2 trials would benefit greatly if a range of doses could be rapidly evaluated. In fact, it is quite feasible that many compounds could produce acute improvements, as have been seen with volunteers in the previous section. To evaluate such effects, short repeatable tests would be necessary, and one recent study suggests this is feasible in AD patients using the CDR system.<sup>33</sup> Here, the acute cognitive effects of intravenous flumazenil were identified in AD patients by assessing them prior to infusion and again at 15, 40, and 240 minutes later. Three tests from the CDR system were employed, two to measure attention (simple and choice reaction time), and a test of episodic secondary memory (picture recognition). This enabled a double-blind, placebo-controlled, single-dose, 2-way crossover trial to be conducted in AD patients, the first time to the knowledge of these authors that multiple repeated testing over so short a period has been possible in AD. The sensitivity of the system was demonstrated by identifying short-term impairments with the compound in two of the tasks, despite the trial only having 11 patients.

## Dementia with Lewy bodies

An important newly identified dementia is dementia with Lewy bodies (DLB), believed to account for up to 20% of all dementias, and previously largely mistaken for AD.<sup>137-141</sup> The condition is known to be more cholinergically specific than AD, and thus more likely to respond to cholinergic treatment. There is also a larger nicotinic component to the cholinergic damage. Here, unlike other dementias, attentional deficits are

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recognized as a core symptom of the disease, and recent work with the CDR system has shown greater attentional impairments in DLB patients than in AD patients, while showing a double dissociation with DLB patients having smaller verbal memory deficits than AD patients.<sup>137-141</sup> The condition can also be differentiated from vascular dementia.<sup>142</sup> In comparative work using the CDR system with four types of dementia, AD, DLB, vascular dementia, and Huntington's disease, it is clear that each has its unique profile of cognitive impairment over the various tasks and measures. Any scales therefore that yield single scores for cognitive impairment will not properly reflect the diversity of the cognitive impairment seen nor the implications of this diversity for the true behavioral profile of the different diseases. The cholinergic nature of the attentional deficits has been further confirmed by comparing nonhallucinators with patients who do hallucinate.<sup>143</sup> It has been shown that hallucinators have greater cholinergic deficits than nonhallucinators, and comparing the two groups on CDR tests of attention showed greater attentional deficits in the hallucinators. Disturbances of consciousness (DCs) are a key clinical diagnostic feature in DLB, while they preclude a clinical diagnosis of probable AD. Despite the prevalence and importance of this key symptom, current identification of DCs relies solely on expert clinical judgement, resulting in poor interrater reliability and inaccurate identification. In one study, 129 patients (37 DLB, 60 AD, and 33 healthy elderly volunteers) with assigned clinical DC scores, were assessed using the CDR 90-second choice reaction time task.<sup>144</sup> Correlations between variability (standard deviation) within the 90-second choice reaction time trial and clinical measures of DC where investigated. Variability in attentional performance across the 90 seconds strongly correlated with clinical DC scores, remaining significant when mean reaction time was accounted for using the coefficient of variation. An optimal cutoff score in choice reaction time variability, derived from the first 35 subjects, discriminated AD from DLB patients with a specificity of 95%. Variability in a 90-second attentional trial appears to be a sensitive, accurate marker for DCs, with substantial implications for the identification and description of this key symptom. These findings have considerable implications for the existing operationalized clinical diagnostic criteria for AD and DLB.

Finally, in the first international therapeutic clinical trial in DLB (ENA-INT-03), in which the CDR system was used as an outcome measure to test the efficacy of the anticholinesterase rivastigmine, a marked and highly significant response to treatment was identified on the CDR tasks, particularly the attentional tasks, which faded when treatment was withdrawn.<sup>145</sup> These effects were large in magnitude and more substantial than those typically identified in AD using the ADAS. This identifies DLB as an important target for future work with drugs acting via cholinergic and particularly nicotinic mechanisms.

## Cognitive deficits in various populations

Using the CDR system, various profiles of cognitive impairment have been seen in a range of clinical and psychiatric populations. A range of deficits in cognitive function has been seen in young first-time-diagnosed schizophrenic patients compared with aged, matched controls.<sup>146</sup> Severe cognitive deficits have been identified in patients suffering from chronic fatigue syndrome<sup>147</sup> as well as patients with multiple sclerosis.<sup>148,149</sup> Milder deficits have been seen in hyperthyroid patients.<sup>150</sup> Diseases associated with the carotid artery can also lead to cognitive impairment, including carotid sinus syndrome<sup>151</sup> and carotid sinus hypersensitivity.<sup>152</sup> Further, cognitive impairment can be identified following carotid endarterectomy.<sup>153,154</sup> Cardiovascular disease can also lead to cognitive impairment. Recent work has shown widespread deficits in elderly hypertensive patients compared with normotensives,<sup>155</sup> and a range of impairments have been seen in patients with various cardiovascular conditions.<sup>156</sup> Cardiac bypass surgery has long been associated with subsequent cognitive impairment, and a recent trial has confirmed these deficits and shown that patients receiving minimal invasive cardiac procedures have little or no residual impairments.<sup>157</sup> Stroke produces cognitive impairment equivalent to mild-to-moderate AD,<sup>158</sup> which, although the symptoms recede over the first 8 weeks, fairly severe deficits still remain at this time. This study also showed that the various CDR measures correlated well with the traditional instruments in this field, the Barthel, the Rankin, and the NIH indexes.<sup>158</sup> Traumatic head injury is clearly associated with severe cognitive deficits,<sup>159</sup> while even minor head injury can be associated with persistent cognitive impairment.<sup>160</sup> Diabetes is associated with fairly marked cognitive impairment.<sup>161</sup> It

is important to note that, as has been seen earlier in this section with different types of compound and different types of dementias, each of these conditions has a different profile of impairments, and while many may show impairments for the same tasks, the relative impairments for the various measures is always different, giving each condition a characteristic profile.

A number of other conditions can induce cognitive impairment. In one trial, junior housemen having worked a weekend on a busy surgical oncology ward were found to show measurable cognitive impairment on reporting to work the following Monday morning compared with Mondays following weekends when they were off-duty.<sup>162</sup> Chemicals found in the workplace have been shown to disrupt functioning. Dentists exposed chronically to mercury were found to have mild cognitive deficits,<sup>163</sup> while workers exposed to solvents on a long-term basis showed severe deficits.<sup>164</sup> Users of ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) have been found to have fairly selective deficits to episodic memory.<sup>165</sup> Carbon monoxide poisoning has been shown to result in severe deficits.<sup>166</sup> Finally, magnetic fields of the type associated with some domestic appliances have been shown to disrupt functioning<sup>166</sup>; and an improvement in choice reaction time was seen with a simulated mobile phone signal, suggesting that mobile phones may alter cognitive function.<sup>167</sup>

In the field of oncology, cognitive testing with the CDR system has proven practical and acceptable. Hospitalized patients taking opioids for cancer pain have been successfully tested,<sup>168</sup> as have patients receiving either chemotherapy of rIL-2 for colorectal cancer.<sup>169,170</sup> rIL-2 was shown to produce marked declines, which reversed following the cessation of immunochemotherapy. Testing was possible daily during three successive 8-day cycles with 14-day intervals. Performance under chemotherapy was extremely stable over the trial, with the large impairments due to rIL-2 returning to preinfusion levels a week later.

Midazolam is commonly used as a preoperative anxiolytic, particularly in dental work. In a recent trial in which the CDR was administered to dental patients, impairments have been shown to be more widespread following midazolam administration than following nitrous oxide.<sup>171</sup> The important contribution of this work to practice in dental hospitals was recognized in an editorial in the same issue of the *British Dental Journal*, which endorsed the recommendation that patients

should receive written instructions on leaving the units due to the persistent amnesia measured by the CDR tests following midazolam. Temazepam is also used as a premedication in day case surgery. In one trial, patients were assessed prior to and several times postsurgery; temazepam or matching placebos being administered preoperatively.<sup>172</sup> The effects of anesthesia were easily detected by the cognitive tasks, as were the additional but temporary impairments produced by temazepam.

### Reversing deficits in various patient populations

In chronic fatigue syndrome, the deficits in attention were shown to be temporarily reversed by the administration of oxygen.<sup>173</sup> In elderly depressed patients, those treated with placebo showed an increase in cognitive impairment on various tasks over a 50-day period.<sup>174</sup> Those who were treated with nortriptyline showed improvements in Hamilton Depression Rating Scale (HAM-D) scores and also showed a smaller decline in performance over the 50-day period. The group of patients treated with moclobemide, however, showed no decline but actually a significant enhancement in performance over the study. This study suggests that the cognitive impairment associated with depression will worsen if it is not treated. Even a tricyclic compound like nortriptyline, which will impair function under normal conditions, will show some degree of improvement as the symptoms of depression are treated and the cognitive impairment remits. However, compounds such as moclobemide, which are free from unwanted effects, and possible cognitive enhancers will improve function in such patients by treating depression and having no liability to compromise efficiency.

In elderly hypertensive patients who were on long-term treatment using the  $\beta$ -blocker atenolol, a trial was performed by switching half of the patients to the ACE inhibitor cilazapril.<sup>175</sup> Cognitive function was assessed using the CDR system over a 20-week period. Significant improvement in choice reaction time and a pattern of enhancement in many other assessments was seen in the patients switched to cilazapril. This trial suggests that  $\beta$ -blocker withdrawal should be considered for any elderly patient showing signs of cognitive dysfunction.

The effects of herbal medicines are becoming increasingly studied as the push towards evidence-based medicine spreads into this field. Ginkgo has been shown to improve function in elderly people with mild cognitive impairment in a 3-month, placebo-controlled, double-

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blind trial.<sup>176</sup> Such effects have also been seen in patients with more severe cognitive decline.<sup>177</sup> Finally, a combination of *Ginkgo biloba* and *Panax ginseng* has been shown to have a dose-dependent benefit in volunteers fulfilling the criteria for neurasthenia, a condition associated with fatigue.<sup>178</sup> The benefits are primarily to memory performance, and the relative contribution of ginkgo and ginseng to these effects is currently under study.

## Conclusions and future directions

Computerized testing of cognitive function has now come of age and is available for any trial in any population. It can be conducted throughout the development process, from the first time the compound is given to man right through the phase 4 trials. The information that such testing can yield is vital to “go–no go” decisions, and the earlier in the development program the testing is introduced, the earlier such information is available and the more appropriate are the decisions made concerning future development. While trials can be designed with the specific intention of assessing cognitive function, cognitive testing can also be integrated into almost any study design without compromising the initial aims of the study.

It is also clear that the concept of independently assessing a variety of cognitive functions has paid dividends in helping differentiate drugs, types of dementia, and different illnesses. Such differentiations are crucial as they permit a unique insight into how the alterations to various cognitive functions will manifest themselves in everyday behavior. This reveals the clear limitation of scales that yield a single score; while such information is rapidly digestible, it does not permit anything but a

quantitative interpretation; and the concept of “more” cognitive function or “less” is manifestly inappropriate for something as complex and diverse as the interplay between cognitive function and human behavior. The next stages for cognitive testing are to achieve independence from the current platform for testing, the stand-alone PC. There are two major opportunities for doing this. The first is to conduct cognitive testing over the telephone, and such a version of the CDR system has been developed and validated,<sup>179,180</sup> and is now in use in clinical trials. Here, a central computer using interactive voice-response techniques presents the test stimuli over the telephone, and the patient responds by pressing the touch keys. Reaction time and accuracy are assessed, and these have shown high correlation with the same tests administered with computers. This system can automatically and simultaneously test over 100 patients in virtually any location. The patients can be assessed at home, at frequent intervals, without the involvement of study personnel or the completion of any paperwork. Further, the data are verified and processed during testing and automatically stored in a central database. This highly efficient system can be used in trials of any size and duration. Clinical research now has a methodology for the remote assessment of cognitive function.

The second opportunity is testing via the Internet. Prototypes are currently running and a full system is expected to be online by early 2001. Again the benefits are the numbers of patients who can be assessed at any time as well as the ease of gathering and verifying the data. This system will be of greater initial utility in North America where a greater number of homes are connected to the Internet. However, it is likely that Europe will catch up in a few years and a second methodology for the remote assessment of cognitive function will be available. □

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### El valor de la evaluación de la función cognitiva en el desarrollo de fármacos

Este artículo revisa el valor y la utilidad de la medición de la función cognitiva en el desarrollo de nuevos fármacos en comparación con el sistema automatizado más ampliamente utilizado en la investigación clínica. Se presenta la evidencia desde la fase I hasta la fase III de la naturaleza y calidad de la información, la que puede ser obtenida al aplicar el sistema de evaluación computarizado de la investigación cognitiva de fármacos a los actuales ensayos clínicos. Se puede obtener una evidencia de gran valor aun en el primer ensayo en que se administra un nuevo compuesto al hombre: una aplicación de esta prueba sirve para asegurar que los nuevos compuestos están libres de propiedades que deterioren la función cognitiva, particularmente en relación con productos de la competencia. Por otra parte se asegura que no ocurran reacciones indeseables con alcohol u otros medicamentos, o si ocurren, se está en conocimiento de ellas. En muchos grupos de pacientes, la disfunción cognitiva se produce como resultado del proceso patológico, y los fármacos más recientes que pueden tratar los síntomas de la enfermedad sin un adicional deterioro de la función pueden a menudo ser beneficiosos al reducir la disfunción cognitiva inducida por la enfermedad. Otra aplicación importante es la identificación de los beneficios de compuestos diseñados para reforzar la función cognitiva. Tales efectos pueden ser explorados en los típicos ensayos de fase I; también el modelo de la scopolamina de los principales déficits de la enfermedad de Alzheimer puede ser utilizado para identificar potenciales fármacos antidemencia. A fin de cuentas, dichos efectos pueden ser demostrados empleando procedimientos automatizados correctamente validados y altamente sensibles en poblaciones blanco. Los datos presentados demuestran que el concepto de la evaluación independiente de una variedad de funciones cognitivas es crucial para ayudar a diferenciar fármacos, tipos de demencia y distintas enfermedades. Dicha información permite un análisis exclusivo acerca de la forma cómo las alteraciones de varias funciones cognitivas se manifestarán en las conductas de la vida diaria. Esto revela una limitación importante de las escalas que entregan sólo un puntaje, puesto que esta información reducida no permite más que una interpretación cuantitativa y el concepto de "mayor o menor" función cognitiva es manifiestamente inapropiado para algo tan complejo y diverso como la integración entre el funcionamiento cognitivo y la conducta humana. Finalmente se describen las futuras generaciones de pruebas cognitivas. La evaluación por vía telefónica se ha introducido recientemente y tendrá efectos significativos en la logística de la realización de pruebas cognitivas en grandes poblaciones de pacientes de ensayos clínicos. La evaluación por vía de internet no está lejos de utilizarse dado el alto número de hogares que se están conectando a la red en Europa y Norteamérica. No hay razones fundadas para no querer incluir las pruebas de función cognitiva en el desarrollo de protocolos de cualquier nuevo medicamento.

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# Clinical research

## Valeur de l'évaluation de la fonction cognitive dans le développement d'une molécule

Quelles sont la valeur et l'utilité de la mesure de la fonction cognitive dans le développement des nouvelles molécules ? Telle est la question traitée dans cet article en référence au système automatisé le plus largement utilisé en recherche clinique. Le système d'évaluation informatisé de " Cognitive Drug Research " sur les études en cours a fait la preuve de la qualité et de la nature des informations obtenues en phase I à III, même au cours de la première étude dans laquelle un nouveau composé est administré à l'homme. De tels essais permettent d'une part de s'assurer de l'innocuité des nouvelles molécules sur la fonction cognitive surtout en ce qui concerne les molécules concurrentielles, d'autre part de veiller à l'absence d'interactions indésirables médicamenteuses ou avec l'alcool ou de les situer dans leur contexte. Chez beaucoup de patients, l'altération de la fonction cognitive résulte d'un processus pathologique dont les symptômes peuvent être traités par de nouveaux produits sans effets délétères supplémentaires et dont le bénéfice se révélera au fur et à mesure de l'amélioration de la fonction cognitive. Certaines molécules permettent aussi d'améliorer la fonction cognitive de base et cette amélioration peut être mesurée. De tels effets peuvent être recherchés en phase 1 des essais cliniques ou bien en utilisant un modèle des principaux déficits cognitifs de la maladie d'Alzheimer induits par la scopolamine dans la recherche des molécules antidéméntielles. Tout compte fait, seules des procédures très sensibles et fiables sur des populations cibles permettront leur mise en évidence. Les données présentées démontrent que le concept d'évaluation des fonctions cognitives de façon indépendante est primordial pour permettre de différencier les thérapeutiques, les types de démence et les différentes maladies. Une telle information offre une perception unique de la façon dont les altérations de la fonction cognitive se manifestent au quotidien. Les échelles à score unique qui n'autorisent qu'une interprétation quantitative montrent ici leurs limites et le concept de fonction " plus ou moins cognitive " se révèle inapproprié pour une notion aussi complexe et variée que l'interaction entre fonction cognitive et comportement humain. En dernier lieu, les nouvelles générations de tests cognitifs sont décrites. Les méthodes de test par téléphone sont récentes et vont bouleverser la logistique des tests cognitifs sur les études à grand effectif. Dans un avenir proche, les tests se feront par Internet, proportionnellement au nombre de foyers connectés en Europe et en Amérique du Nord. Il n'existe pas de raisons valables de vouloir exclure les tests des fonctions cognitives du développement de la médecine du futur.

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