



The use of cognitive tests to facilitate drug and dose selection in Phase I and to optimise dosing in Phase IV

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Abstract

The age of automated testing of cognitive function has now been with us long enough for such testing to be considered traditional. Properly automated test systems enable function to be assessed rapidly, definitively and sensitively. Such test systems can be easily incorporated into the busy experimental designs which characterise Phase I. This paper will present data from the Cognitive Drug Research (CDR) computerised assessment system. There are a variety of reasons for measuring the effects of novel compounds on cognitive function early in drug development. Obviously, the absence of cognitive toxicity is one important feature for the development of novel treatments for many CNS and non-CNS illnesses, and the potential waste of considerable time and money can be avoided by identifying unwanted effects as early as possible. Further, the absence of effects can be considered a 'Proof of concept' for novel compounds that the structure and preclinical work would predict to be potentially free of such effects in man. Cognition enhancers can be confirmed to be active, the nature of the cognitive effect profile can be identified and the nature of the relationship of dose to effect quantified. Cognition enhancement can be established even in first-administration-to-man trials; an advantage of such trials being that they enable effects to be evaluated over the largest dose range that is likely to be administered in the development program. However, due to the small numbers of volunteers involved in first-to-man work, it may require a subsequent study to establish the optimal dose range, and this could be necessary before multiple dosing. The scopolamine model has shown utility in screening anti-dementia drugs and, while being particularly sensitive to anticholinesterases, has also shown utility in evaluating a wide range of compounds. Finally, a technique for administering the CDR system over the telephone has recently been developed and validated and is now in use in clinical trials. This system will have considerable

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utility and value in facilitating the assessment of cognitive function in late phase research. © 2001 Elsevier Science B.V. All rights reserved.

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1. The assessment of cognitive function

Cognitive function refers to the mental processes that are crucial for the conduct of the activities of daily living. Cognitive function includes the processes of attention, working memory, long-term memory, reasoning, coordination of movement, planning of tasks and so on. The efficiency with which these processes are operating has a direct influence in how well everyday activities are conducted. Psychologists have long sought both to understand how these processes operate and also to measure them. It is the measurement of cognitive function, which will be of principal relevance to this paper.

Mood states are often misinterpreted as being aspects of cognitive function. While cognitive function can be influenced by mood states, mood states themselves are independent subjective experiences, which can best be assessed by the volunteer or patient completing rating scales or undergoing a clinical interview. In psychopharmacology, it is important to determine the extent to which changes in mood may account for changes in performance of cognitive tasks and instruments such as the Bond–Lader Visual Analogue Scales or the Profile of Mood States are particularly useful here.

The measurement of cognitive function involves the assessment of how well a particular aspect of cognitive functioning is operating. This is done by getting a person to perform a task that involves the aspect of cognitive function in question. The quality of measurement will principally depend on how demanding the task is, its specificity to the particular aspect of function being assessed and how comprehensively task performance can be measured.

Criticisms of many traditional tests are first that they confound a range of cognitive functions and second they are not able to rule out speed–accuracy trade-offs. Consider the Digit Symbol Substitution Test (DSST), one of the most widely used pencil and paper tasks in psychopharmacology. In this task, volunteers have a set time in which to copy as many symbols as possible into boxes (substitutions) according to a code on the top of the sheet. This task requires at the minimum, attention, working memory and skilled coordination, yet yields a single primary score, the number of correct substitutions. Therefore, any changes in this score cannot be unequivocally attributed to any one of these aspects of cognitive function. Further, there are no agreed quality criteria for how well the symbols need to be copied, and thus a volunteer could on one occasion be very precise in copying the symbols, and on another occasion take less time and be less precise. In the latter case, the individual will complete more substitutions in the time allowed, and thus the score will be considered to be superior to the previous one. This will clearly lead to misinterpretations, as the quality of cognitive function could easily

have been identical on the two occasions the task was performed, the difference being in the volunteer's strategy. This inability to identify speed–accuracy trade-offs is a major limitation of many non-automated tasks.

Other widely used tasks do not measure cognitive function in the first place. For example, the widely used Critical Flicker Fusion (CFF) task actually measures a psychophysical threshold, i.e. the frequency at which a flickering light source can no longer be perceived to be flickering. This threshold, like other perceptual thresholds, e.g. auditory and pain thresholds, is largely independent of cognitive function. The problem here is that changes may occur to these psychophysical thresholds which have nothing to do with changes to cognitive function; for example CFF may change due to impairments to the visual system itself. Thus, while CFF and aspects of cognitive function such as attention may correlate at times, they may also dissociate at other times. CFF can at best then be seen as a marker for cognitive function as opposed to a direct definitive measure.

Similar arguments to those above can be made for techniques which measure various aspects of the bioelectrical activity of the CNS, such as EEG, PET and MRI. While these measures reveal much about the functioning of the CNS in themselves, they do not directly measure cognitive function itself. Therefore, the changes in brain functioning identified by these techniques may or may not be directly related to cognitive function, and thus they are indirect assessments. However, they can be directly integrated with cognitive function assessment, and when this is done the joint assessments of function and activity become very powerful measures of change.

2. The automation of tests of cognitive function

Section 1 outlined a number of basic principles that are crucial to the proper assessment of human cognitive function. These can be summarised as follows:

1. There are major areas of cognitive function (e.g. attention, working memory, episodic secondary memory, the control of movement etc) which underpin everyday behaviour.
2. These can only directly be assessed using tests of cognitive function.
3. As far as possible, these tests need to independently assess these various functions.
4. The tests must yield sufficient information such that the interpretation of any change can be made definitively, and in most cases this can only be done by assessing speed as well as accuracy of performance.

The Cognitive Drug Research (CDR) automated assessment system was developed to provide a system which satisfied these requirements. The CDR system has its roots in the automation of tests in the 1970s [1] initially on a Mini-Computer (the PDP-12) and then on one of the early microcomputers (the RML 380Z). In the early 1980s, the system was installed onto the BBC microcomputer and validated first in young and then elderly volunteers. In the mid-1980s, to facilitate the use of the CDR system worldwide, the system was moved to the IBM PC platform where it still remains (a Windows

version is being released in the autumn of 2000). The system has a core set of tests which can be supplemented by a wide range of additional procedures (e.g. logical and semantic reasoning, rapid information processing, tests of motor function and postural stability, psychophysical thresholds, e.g. CFF, and assessments of mood and alertness). It also has the ability to facilitate and control the administration of a wide variety of traditional tests including pencil and paper tests. The automated tests available in the system are listed in Table 1.

The keyboard is not used in any test; most tests involve responses made via a customised 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 (1–3 min, although some tasks can be extended for special requirements). Different versions have been developed and validated for volunteers (young and elderly) and various patient populations [2,3]. Testing can be directly linked to EEG and evoked potential recording in order that behavioural and electrophysiological effects can be integrated [4]. The utility, reliability and validity of the system have all been exhaustively demonstrated and discussed (e.g. Refs. [2,5–7]). Over the last 15 years, its use has become widespread in many fields, and it is now the most widely used automated system of its type in worldwide clinical research.

Table 1.

The tests available in the CDR system listed under the aspect(s) of cognitive function they assess

Attention

Simple reaction time
Choice reaction time
Digit vigilance

Executive function and working memory

Articulatory working memory
Spatial working memory
Rapid visual information processing
Logical reasoning

Episodic secondary memory

Word recall
Word recognition
Picture recognition
Face recognition

Motor control

Joystick tracking task
Tapping task
Postural stability task

Psychophysical thresholds

Critical flicker fusion (with and without pupil size control)

3. The demands imposed on cognitive testing procedures in Phase I trials

Early Phase I studies are by their nature busy, intensive and often invasive. In first-administration-to-man trials, a large number of different types of assessments are fitted into the study day. Infusions are sometimes used, plasma samples regularly taken and a variety of safety procedures administered at frequent intervals. Multiple dose trials also have some very intensive study days. Phase I trials are usually carried out in cohorts of between six and nine volunteers. In most Phase I Units, volunteers are housed in wards, and the majority of the procedures performed there. This together with the intensive nature of the study days puts clear constraints on the types of tests which can be administered. Firstly, the frequency of plasma sampling and other procedures limits the duration of time available for cognitive tests. In most first-administration trials, no more than 15-min intervals are available for cognitive testing in 2 or 3 h following administration. Thus, one clear requirement is that the tests must be short in duration. Secondly, testing is ideally conducted in study rooms off the main wards, where the background noise and other environmental factors can be controlled. Very few centres have individual cubicles available for testing, and thus such testing is generally performed in rooms in which the required number of workstations can be set up. A single experimenter can supervise testing, setting each machine up for the next volunteer due. Generally, there is a dose-stagger of around 5 min, and thus volunteers are brought individually to the testing room; a group of eight volunteers for example can generally be tested in this manner with four workstations plus a spare. Sometimes the volunteers need to remain in bed, either because of infusions or due to other assessments. In this case, the testing is conducted by laptop computer. Considering these environmental conditions, it is clear that tests which require continuous one-to-one administration are rarely feasible in Phase I. First, it simply is rarely if ever practical to have one tester per volunteer, and second, the nature of most one-to-one tests precludes their use in this environment; for example, memory tasks which involve repeated oral presentation of word lists and oral responses (such as Buschke Selective Reminding Learning Task, California Verbal Learning task, Rey, etc.), or tasks which require spoken responses by the volunteer, e.g. Stroop task, category fluency, etc. It is obviously not appropriate for other volunteers to hear items they may be required to remember and the general noise from these and other spoken tasks may distract them anyway. On the other hand, properly automated tests are ideal in such situations. The volunteer is taken to his/her machine and some preliminary quality assurance checks are made to ensure that this is the correct volunteer to be tested. After this, the computer takes over, presenting the instructions, controlling each task, gathering and then automatically storing the responses. At the end of testing, the volunteer leaves the room, the tester goes to the machine and saves the data on backup disks and prepares the machine for the next volunteer. The computer automatically selects the appropriate parallel form to be used for each successive test session and can warn the experimenter if incorrect information is entered. The CDR system has now been used in hundreds of Phase I studies, and an environment or study has not yet been encountered in which testing could not be performed.

4. Testing for the absence, or relative absence, of cognitive toxicity

Historically, most types of drugs to treat CNS disorders (anxiety, depression, schizophrenia etc) and also non-CNS medications (e.g. antihistamines) have produced impairments to human cognitive function which have disrupted the ability of patients to undertake the activities of daily living. Clearly in populations where cognitive function is already compromised, e.g. the elderly, demented or schizophrenic patients, such effects can pose very serious problems. One potential advantage of many newer medicines under development is to be relatively free from such unwanted effects. Such effects (or confirmation of their absence) can be sought in the early stages of drug development, even first-administration-to-man trials. The selection of tests in the latter type of trial should generally be restricted to the core tasks for each area of function and ideally will last around 15 min or so. There are several advantages of incorporating cognitive testing into first-administration-to-man trials. One is that the range of doses studied is almost invariably the widest which will be administered in the development program, and thus this is an ideal opportunity to establish the pharmacodynamic relationship over such a dose range. If no effects are identified even at very high doses, this is a very likely indication that none will be encountered with smaller single doses for the rest of the development program. Another advantage of gathering some early information about the potential cognitive effects of a compound occurs when a compound shows safety or tolerability problems or poor pharmacokinetics, and development is stopped. In such cases, the information about the cognitive effects (or lack of them) will aid the decision process as to 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 GABA_A receptor agonist at some receptor subtypes and a partial agonist at others. ME3127 was studied in a first-administration-to-man double-blind, placebo-controlled, escalating, single oral dose study in 56 healthy young volunteers [8]. CDR tests were completed at predose, and at 2, 4, 8 and 24 h postdose. A dose-dependent range of impairments was detected, the highest dose having clearly identifiable effects on a range of measures. The profile and magnitude of these effects was compared to the CDR database, which identified that peak impairments produced by ME3127 on attention and working memory resembled those of lorazepam 1 mg, while those on secondary memory and self-rated alertness resembled those seen with lorazepam 2 mg. This showed that the compound was acting differently to the benzodiazepines and put in context the extent of the impairments which might be expected. In a follow up study [9], multiple doses of ME3127 were studied and repeated testing was performed on days 1 and 9 of dosing. 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 and secondary memory tasks some improvements were seen.

NS2389 acts by blocking the neuronal uptake of 5-HT as well as other monoamines such as noradrenaline and dopamine. The CDR system was used to study the compound in a range of single doses of in a double-blind, placebo-controlled, study in 64 healthy male

volunteers [10]. Some evidence of impairment was detected at various doses in this study though these effects were not marked.

A selective M₃ 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 nine-day multiple dosing study [11]. One potential advantage of selective M₃ receptor antagonists is that they should be relatively free from the unwanted cognitive impairment seen with existing non-specific anticholinergic treatments. The CDR system was administered six times per 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 on the dose range over which no cognitive impairment would be seen in patients.

Another common procedure in Phase I 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 D₂ antagonist and 5HT_{1A} agonist properties was compared to buspirone 30 mg using the CDR system in young volunteers [12]. 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.

In another trial, 18 healthy male volunteers took part in a six-way cross-over trial to contrast DU 29894 (3 and 10 mg), a novel D₂ antagonist/5HT_{1A} agonist, with sulpiride 400 mg, haloperidol 3 mg and flesinoxan, a novel selective 5HT_{1A} agonist [13]. All 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 each other. Overall, haloperidol produced the greatest impairments.

A group of 14 elderly volunteers were dosed for 4 days with either haloperidol 3 mg, olanzapine 3 mg or placebo in a three-way cross-over design [14]. 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 h of washout. In contrast, haloperidol showed a smaller overall impairment on the 1st day which had increased dramatically by the 4th day and was still marked on many measures after 48 h 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. Importantly, despite being markedly impaired with haloperidol after 48 h of washout, the volunteers reported no lowering of self-rated alertness compared to predosing, emphasising the importance of objective tests of ability.

Remacemide, a noncompetitive NMDA antagonist under development for the treatment of epilepsy, was found to have dose-dependent cognitive impairment in acute doses up to 400 mg in a five-way placebo-controlled cross-over design with 16 young volunteers [15]. 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 [16]. This suggests that for some compounds, such as ME3127 and olanzapine mentioned previously, tachyphylaxis for cognitive impairment can occur with repeated dosing.

5. Cognition enhancers

Most pharmaceutical companies are developing cognition enhancers. There are a wide variety of obvious targets for such compounds, including dementia, stroke, head injury, attention deficit disorder, ageing and so on. Apart from occasional compounds which might have specific mechanisms of action to treat or help retard specific neurodegenerative disorders, most compounds are likely to have the capability of improving normal function. If such effects can be determined early in development, this is extremely important as it confirms the activity of a compound, something possible in Phase I with very few classes of compounds.

The CDR system has identified cognition enhancement in several Phase I 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, was studied in a first-administration-to-man safety and tolerability trial [17]. The compound produced a wide range of enhancements on CDR assessments, including improvements to attention, working memory and episodic memory, as well as increasing self-rated alertness. These effects were obtained although only six volunteers received each active dose and four received placebo. The effects appeared particularly long-lasting, and in a follow up trial [18], higher doses were studied and effects were assessed up to 360 h following a single dose. Benefits were seen which were of the same profile as seen in the previous study and, remarkably, some benefits were seen at 360 h. In another first-administration-to-man trial, a range of doses of NS2359, a noradrenaline, dopamine and serotonin reuptake inhibitor, was studied in 56 volunteers [19]. The compound showed clear cognition enhancing properties particularly 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-seven nicotinic receptor [20]. A clear profile of enhancements was seen to attention, working and secondary memory. This profile was unexpected, as the effects of nicotine are primarily limited to attention and information processing; no convincing evidence of beneficial effects of nicotine on memory having been identified (e.g. Ref. [21]). This suggests that the selectivity of the compound to the alpha seven subtype of the receptor is a particularly promising avenue for cognition enhancement. Finally, in a cross-over study with 12 young volunteers, the anticholinesterase physostigmine was found to produce a range of en-

hancements to attention and episodic memory [22]. This is one of the few 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 [23], though generally there is little systematic evidence that the elderly respond more readily to cognition enhancers than the young [24]. In one trial, S-12024, a pro-noradrenergic compound with nicotinic agonist properties was found to improve cognitive function in a multiple dose safety and tolerability trial [25]. Interestingly, here the improvements occurred in aspects of function which had declined when the population was compared to younger volunteers. Further, the most effective doses were 50 and 100 mg, the lowest and highest doses (10 and 200 mg) being relatively ineffective. Such an inverted-U profile is commonly seen in animals but less often in man. Nonetheless, this provided excellent evidence that in patient work, simply dosing to the maximum tolerated dose would not probably not be the optimal strategy. In another study, HOE 427, an ACTH_{4–9} analogue, was found to produce some evidence of improvement in a four-way cross-over design in 20 elderly volunteers [26].

Serendipity can also play a part in drug development. The CDR system was included in trials of flesinoxan, a 5HT_{1A} agonist, 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 some evidence relevant to the debate referred to in the previous paragraph [27]. Further, in trials which have been conducted to identify potential interactions between alcohol and novel compounds, beneficial effects of the study compounds when administered alone have been identified. Such findings have occurred for moclobemide [28,29], sibutramine [30] and SB-202026 [31].

The opportunity of including patients with dementia in Phase I trials is particularly attractive for rapid confirmation of ‘proof of concept.’ The CDR system was used in a single dose, placebo-controlled, double-blind, cross-over trial of the benzodiazepine antagonist, flumazenil, in 11 Alzheimer’s patients [32]. Testing was conducted before dosing and at 15, 40 and 240 min after dosing. Effects were seen at 15 min, though they were impairments in performance, not enhancements as might have been expected. Nonetheless, this is a clear illustration that rapid information on cognitive effects of novel compounds could be obtained in demented patients in Phase I.

6. The scopolamine model of dementia

The scopolamine model is another method for screening cognition enhancers designed to be anti-Alzheimer’s drugs. In the mid-1980s, there was a growing recognition that cholinergic deterioration underpinned some of the major cognitive deficits in Alzheimer’s disease, and when this information was put together with the similar impairments produced by the cholinergic antagonist scopolamine in volunteers, it led to the idea that scopolamine could produce a model of some of the core cognitive deficits in Alzheimer’s disease. This idea was further developed when nicotine was found to reverse the effects of

scopolamine on attention in young volunteers [33]; the model then becoming a method for identifying the potential of compounds to reverse the effects of cholinergic blockade. The opportunity has thus existed for over 15 years to utilise a model to help screen potential anti-Alzheimer's drugs in Phase I. The validity of this model has been widely established [34–36] and a wide variety of drugs have been screened.

The model is particularly sensitive to anticholinesterases, for example physostigmine 2 mg s.c. has been found to rapidly and completely reverse the impairment produced by scopolamine on all CDR tasks employed [37]. Importantly, these effects were only temporary and had faded 1 h later, which closely mimics the clinical situation, many early trials showing brief improvements to Alzheimer's 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 and linearly dose-dependent [38]. This latter finding is important as it would encourage the evaluation of higher doses in patients. Velnacrine, an analogue of the anticholinesterase tacrine, was found to produce widespread reversal of the cognitive impairment on CDR tasks produced by scopolamine [39]. The drug was then administered to Alzheimer's patients in a Phase IIA trial and improvements were seen on CDR tasks on which reversals had previously been identified in the scopolamine model [39].

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 [40], as has tenilsetam [41], though 3OH-aniracetam (Ro 15–5986) showed no activity [42]. The monoamine oxidase inhibitor moclobemide has been shown to reverse the effects of scopolamine [42], as has the novel compound FK960 [43] as well as D-cycloserine (a partial agonist at the strychnine insensitive glycine site on the NMDA receptor) in both young and elderly volunteers [44,45]. The effects of the latter compound were particularly interesting, as they were limited to the working and episodic memory effects of scopolamine. They were also very specific to one dose, 15 mg, lower and higher doses proving ineffective (5 and 50 mg). Interestingly, D-cycloserine 15 mg was subsequently found to improve implicit memory in Alzheimer's patients [46].

7. The administration of the CDR system over the telephone

In conjunction with ClinPhone, CDR has installed a number of its core tests onto an Interactive Voice Response System. Here, a central computer 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 in a large cohort of volunteers aged 12–85 [47]. The sensitivity of the telephone system to age effects has also been identified, as has its sensitivity in identifying the effects of a low social dose of alcohol (0.5 g/kg). It is currently being used in clinical trials of chronic fatigue syndrome [48], dental patients treated with midazolam [49] and patients with depression. The utility of the system in late stage clinical trials is particularly clear. 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 allows trials with large cohorts such as Phase IV studies to include sophisticated assessments of cognitive function, and will provide much valuable information about the long-term effects of various compounds and also optimal dosing regimen.

8. Conclusions and future directions

Computerised 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 IV trials. The information that such testing can yield is vital to go–no go decisions. The earlier in the development program cognitive 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 behaviour. This reveals the clear limitation of scales which 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 behaviour.

For late phase patient studies, the ability to assess cognitive function remotely over the telephone will greatly facilitate the acquisition of such data and consequently promote the widespread assessment of cognitive function in such work. Such data gathered in trials of this size will permit the identification of optimal doses, long-term effects missed in earlier trials and the discovery of sub-groups who respond in particularly marked fashions to novel medications.

Appendix A. Discussion 4

A. Breckenridge: How important are defects in cognitive function in the clinical manifestations of diseases like anxiety and depression? And can your tests distinguish tests of cognitive function from the other manifestations of these conditions?

K. Wesnes: We think so. We have some data on elderly people with depression from the moclobemide trial and here we were able to identify pre-existing slowings of function. Actually, depressed people seem to have retarded cognitive function, they think and process information more slowly, but actually the quality of what they recall is pretty good. It is a relatively selective speed effect. You can identify this if you look at the

effects of classic therapies such as nortriptyline. Initially, the patients have some cognitive impairment, but as the drug starts to treat the condition, we can identify an improvement in these cognitive symptoms; and if you have antidepressants, like moclobemide, which do not have any negative effects upon cognitive function, you can actually see benefits occurring quite early in the treatment process. Schizophrenia is the same. It is a condition which has cognition impairment as part of its profile and if you can treat the condition without impairing cognitive function further, then you can actually identify quite rapid improvements. I think that is why in many clinical trials, olanzapine has shown benefits: it does not actually enhance function in any way, but it does not damage cognitive function with repeated dosing in the way that haloperidol does, and thus as schizophrenia is treated, cognitive processes return to normal which therefore enables people to function far more appropriately.

W. Evans: Some of the treatments of paediatric cancer are known to have effects or they are thought to have effects on cognitive function of these patients. I'm wondering, has your method been adapted to children?

K. Wesnes: It certainly has utility with children. I used to take my 7-year-old daughter around to show people the testing when they doubted whether patients could do these tests. The youngest person who was tested over the phone was 8 years old. With children, you should avoid very long or infrequent words in some of the tests; but the attentional tests and the coordination tests are very attractive to children and you can make good assessments. So, we do plan to introduce our test system into trials with young people over the next few years. And certainly we have shown that patients with cancer can repeatedly be tested. We had a trial with rIL-2 therapy where we showed, while the pulses of rIL-2 therapy were undertaken, that cognitive function became increasingly impaired but as soon as the therapy stopped, performance returned to base line. So such testing is highly feasible in this population.

S. Jackson: Can I ask you for your current, state-of-the-art views on the use of imaging as a way of screening for drug effects.

K. Wesnes: I think imaging can do things nothing else can. I think that looking for early effects in drug development, MRI can tell you functional things and SPECT can look at receptor occupancy; and so these techniques can give you fantastic information—and we have some very exciting recent data we cannot unfortunately share just now. Linking cognitive function and imaging together and correlating the assessments gives you a very powerful model for identifying cognitive effects. I personally do not think that imaging alone helps assess cognitive function any better than cognitive function tests, but when they are linked together, you get the physiological change mapped in with the behavioural change and it forms a very powerful combination. But imaging can also provide information which cognitive function cannot, obviously because there is a wide range of CNS effects which can be assessed, such as mood effects, which do not necessarily manifest themselves in performance changes, and therefore for which cognitive function testing is not appropriate.

N. Holford: I have a particular interest in drugs in Alzheimer's disease where the standard method for assessing cognitive state is ADASC, the Alzheimer's disease assessment scale. It's used for regulatory purposes and has been, I think, the basis for approval of the few drugs that have made it onto the market. Now, the time course of changes in

cognitive function measured by ADASC for those drugs suggests that it takes 6, 8, or even 10 weeks to reach maximum effect on particular dose. Very different from the kinds of predictions you would have made in the physostigmine studies. Do you think that's because ADASC doesn't really measure cognition over 12 weeks, or is there some mechanism involved other than cholinesterase inhibition?

K. Wesnes: The ADAS-Cog primarily measures memory, and therefore falls down badly because it does not assess attention. We know that cholinergic blockade impairs attention, that Alzheimer's patients have attentional deficits, that physostigmine and other anticholinesterases improve attention as well as memory; but if your marker for cognitive improvement is just measuring memory, as the ADAS-Cog does, it is not measuring the full therapeutic potential of the compound. That is one difficulty. Another is that it is a non-automated procedure, and therefore is not as sensitive as computerised tests. A group in Canada compared our tests to the ADAS-Cog, and a number of other widely used non-automated tests, and showed that computerised testing was better able to actually identify Alzheimer's patients which confirmed it to be more reliable overall. I think often pharmaceutical companies do not conduct the ADAS-Cog for 4 or 8 weeks into Alzheimer's trials, and so the comparison is slightly unfair in that case. Certainly, anticholinesterases have the ability to produce acute effects, there is no doubt about that, and if you include the testing at earlier intervals you can measure these effects sooner. The advantage of computerised tests is that you can administer them every day for a month if you wish. But you couldn't administer an ADAS-Cog anything more than maybe 2 or 3 weeks apart because it is a long procedure with limited parallel forms, heavy interview time and is very tiring for the patients. Those of us on the International Working Group for Dementia Drug Guidance feel that computerised techniques should be used alongside it in clinical trials, and hopefully those procedures which show better utility will be used in the future. Just to finish the answer, the FDA tried to define Alzheimer's as something that happens over 6 months—conceptualising it as an impairment which may be reversed—and shifting thought away from it being something in which you will get absolute improvement. Therefore, the focus of interest has been slowing that stage down but we have got a paper which has just been accepted by *The Lancet* showing that in another type of dementia, Dementia with Lewy Bodies, you can show marked and highly significant improvements. These people become better than they were before, and if they were not treated, they became significantly worse than they were before the trial.

L. Sheiner: I have long wondered about the tendency we all have to look at secondary sorts of things like biochemical tests or EEGs when what we are interested in is how the brain is functioning. Perhaps there was some worry about objectivity versus subjectivity, although if so, there may be an epistemological problem, as attention, for example, would appear to have only a subjective meaning. Perhaps, though, the issue was reproducibility? If so, I wonder if you could say a little bit more about that. Are computerised tests going to be more reproducible than biochemical tests or EEGs? Are there situations in which they change, for example with mood, so that they would be misleading?

K. Wesnes: I think you are right. What got me started in this field developing tests in the early 1970s was that there just were not adequate tests around, and the ones that were around probably did not definitively measure cognitive function, had poor test–retest reliability, perhaps only one or two parallel forms, and so you could not use them to chart

the course of things in clinical trials. In the early 1970s and a good deal of the early 1980s, there were not the right tools around to assess cognitive function. Those of us in cognitive psychopharmacology who work with computerised tests believe that this is an appropriate way to get more definitive, more measurable, more valid and more reliable tools. We can now actually provide clinicians with information relating to clinical effect size. We now have got databases, and when someone asks: "25 ms, what does that mean in clinical terms?" we can reply "actually that effect size is what you would get from a milligram of lorazepam, three units of alcohol, or 22 years of ageing." I think nowadays we can convince people who are consumers of this information that this way of measuring function directly is better than scales or indices. But that has only really happened in the last 12 or 13 years because that is the time period during which we have had the right tools, the right microcomputers which we can just simply take anywhere to test patients. Nowadays, I think cognitive function testing is the best direct measure but as I answered in the previous question, when you start linking them into other assessments, then you get a hugely powerful overall procedure.

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