Assessing cognitive function in clinical trials: latest developments and future directions

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Properly developed automated test systems are of value for assessing changes in cognitive function in clinical trials. Besides the other advantages that automation brings to trials, such as increased reliability and utility, it is shown that such systems are also more sensitive to change in cognitive function than traditional nonautomated procedures. Data from a variety of topical areas in drug development are presented to illustrate the added value such techniques have brought. The latest developments in automation include remote testing via the Internet and telephone.

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The interest in assessing cognitive function in all phases of drug development has never been greater. For novel compounds in a range of fields, it is increasingly important to demonstrate that they are free, or relatively free, of the unwanted cognitive impairment that limits the clinical use of the existing therapies they are designed to replace. In many other conditions, such as depression, schizophrenia and epilepsy, it is becoming increasingly recognized that cognitive impairment is either part of the clinical condition or a consequence of it, and compounds are being sought that not only treat the primary symptoms, but also reduce the cognitive impairment or, at the minimum, do not further exacerbate the problem. In Alzheimer's disease (AD), it has recently been acknowledged that impairments to attention accompany the memory loss, and work is now underway to determine the extent to which these attentional impairments can be rectified by novel and existing therapies. A new form of dementia, Dementia with Lewy bodies, actually has attentional impairment as a core symptom, and the first properly conducted clinical trial in this condition has shown a dramatic response to treatment with an anticholinesterase. This dementia shares some of the neurochemical and neuroanatomical pathology of Parkinson's disease (PD), and this work also suggests that the cognitive impairment that develops in elderly Parkinson's patients could also be treated. Phytopharmaceuticals are becoming increasingly popular and substances such as ginkgo are consistently being shown to improve function in a range of populations, from young volunteers to patients with dementia. The Efficacy Working Party of the European Medicines Evaluation Agency (http://www.emea.eu.int) has recently specified the use of cognitive testing in a variety of neurological and psychiatric disorders.

Much of the progress made in these various fields has been the result of introducing automated cognitive testing systems into clinical trials. Some systems have now been in use for >15 years and have large databases. Such systems have greatly facilitated the ease, quality and sensitivity of testing and have enabled effects to be identified, which previously went unnoticed with traditional pencil and paper tests. Automated cognitive tests are now routinely applied in early drug development by many pharmaceutical companies and can identify both unwanted cognitive impairment (or its absence), as well as cognition enhancement. Furthermore, properly developed automated tests have been widely applied to patients with various dementias, yielding valuable insights into the nature of the cognitive deficits and also the response of these deficits to therapy. Recent technological advances in automation include testing via handheld computers, administering cognitive

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tests automatically over the telephone and testing via the Internet. These innovations will have a dramatic impact on the application of automated testing to large Phase III and IV programmes in many areas of drug development.

Cognitive function assessment

Cognitive function refers to those mental processes that are crucial for the conduct of the activities of daily living. Such mental processes include attention, short-term (working) memory, long-term memory, reasoning, the coordi nation of movement and the planning of tasks. All of these processes vary in how well they are operating; sometimes our attention is poor, sometimes our memory seems excellent, sometimes we plan our activities badly, and so on. Therefore, the efficiency with which these processes are operating clearly has a direct relationship to our ability to conduct everyday activities and, thus, ultimately influences important aspects of the quality of life.

The study of cognitive function is an important branch of psychology. In drug development, as in other fields, it is the responsibility of psychologists to measure cognitive function. This is achieved by getting volunteers or patients to perform tasks that involve the particular aspects of cognitive function in question. The quality of such measurement will depend on the quality and sensitivity of the tasks. A very important control is to ensure that changes in performance of the tasks reflect the quality of operation of the particular aspect of function under study, and not peripheral changes, such as alterations to visual acuity or changes in mood states, such as anxiety. Historically, the assessment of cognitive function in drug development has been dogged by a host of problems, including the failure to implement such controls and the use of inappropriate and/or insensitive tests. A further problem has been the administration and interpretation of cognitive tests by untrained and unqualified personnel. Although a psychologist without medical training would not, for example, presume to administer or interpret an ECG, researchers from almost any field outside psychology frequently administer and describe the results of cognitive tests, with all too often sadly predictable consequences.

Over the past three decades, psychologists have sought to improve the quality of cognitive function assessment in drug development. There is now an emerging discipline of Human Cognitive Psychopharmacology, the fundamental tenets of which are:

(1) There are major areas of cognitive function (e.g. attention, working memory), which underpin everyday behaviour.
(2) These can only be assessed directly using tests of cognitive function.
(3) These tests need to assess these various functions independently, as far as possible.
(4) The tests must yield sufficient information and be conducted with sufficient controls such that the interpretation of any identified change can be made definitively.

Neuropsychology is another branch of psychology in which a wide range of tests of cognitive function is used. The tests are generally applied to patients with cognitive deficits caused by trauma or other insults, the requirement being to identify and quantify the precise nature of the cognitive impairment. Some of the tests used in neuropsychology have been adapted for use in psychopharmacology but others are not commonly used because of the differing methodological requirements of the two fields. Generally, in neuropsychology, patients are assessed on a one-to-one basis, and often only assessed once. In psychopharmacology, volunteers and patients are trained on the tests before the start of the study and are then tested repeatedly over a study period, often in groups. Many test procedures used in neuropsychology are then not appropriate for such clinical trials, particularly when there are few parallel forms of the tests or trained specialists are required to administer them.

Within psychopharmacology there is a significant group of researchers that believes testing should be automated as far as possible [1]. Automated tests of cognitive function have made large advances since the introduction of these procedures to drug development programs in the early 1980s, and have shown much benefit in terms of practicality and sensitivity. Besides not possessing many of the limitations of many traditional tests, they are also generally more sensitive to changes in cognitive function. For example, in a trial of the cognitive effects of interleukin-2 (IL-2) therapy in patients with advanced colorectal cancer, a battery of automated tests was compared to several traditional pencil and paper tests, including the Digit Symbol Substitution Test, the Benton Visual Retention Test and the Trail Making test [2,3]. The automated tests were administered daily for eight successive days during each of three IL-2 cycles administered over a 10-week period. The tests were also administered at weekly intervals between cycles. The traditional tests were only administered weekly throughout the study because of limitations in the number of available forms of the tests. Five of the six computerized tests showed clear impairments during the IL-2 cycles, which reversed a week later: these effects were seen up to the third cycle for several measures. The Digit Symbol Substitution test showed effects in the first two cycles, whereas the Benton test showed no effects, and only form B of the Trail Making test showed an effect, and then only

in the first cycle. Also, because of training effects on the Digit Symbol test, the impairments did not reverse at the end of the cycles. In a recent trial of rivastigmine in Dementia with Lewy Bodies, to be described later, automated tests detected clear beneficial effects of treatment, which were not identified with a number of pencil and paper tests [4]. A further study comparing the sensitivity of an automated test battery to a range of nonautomated tests (Alzheimer's Disease Assessment Scale, Wechsler Memory Scale, Mini-Mental State Examination and Mattis Dementia Rating Scale) in patients with AD and Huntington's Chorea found that the automated tests not only better discriminated between the two types of dementia but also were more reliable in classifying the dementias [5]. Finally, in a volunteer trial, automated tests were more sensitive to the cognitive effects of morphine than the Digit Symbol Substitution Test [6].

Automated cognitive-testing procedures, if properly developed and validated, can facilitate testing in clinical trials and also increase the sensitivity of assessment over traditional methods. The following sections will outline a range of applications of automated tests to clinical trials. The reader is strongly recommended to read a related article by John Harrison, which has just been published [7].

Improving the efficiency of the drug development process

Over the last few years, an 'age of reason' has finally begun in drug development. In contrast to the policy of 'wait and see' that pervaded drug development up until the early 1990s, most developers now wish to know as soon as possible whether the compounds they are developing have desired effects and, at the same time, whether they are also free of undesired effects. In terms of cognitive function, examples of desired effects are for cognition enhancers to be capable of improving cognitive function, or for sedatives, hypnotics and anaesthetics to be capable of impairing cognitive function. By contrast, undesired effects are mainly cognition impairment in compounds hoped to be free of such effects, or cognitive impairment that persists longer than is desired.

Cognitive-function testing is now regularly included in Phase I trials, even in first-administration-to-man trials. Although early Phase I studies are, by their nature, busy, intensive and often invasive, cognitive function testing can be included, provided the appropriate types of tests are employed. In most Phase I units, volunteers are housed in wards, where the majority of the procedures are performed. This, together with the intensive nature of the study days, puts clear constraints on the types of tests that can be administered. Properly computerized tests are ideal, as verbal instructions or responses are not required and a single experimenter can simultaneously test several volunteers, whereas many traditional techniques, by their interactive nature, are inappropriate and/or impractical. Brief but sensitive tests are ideal, and in ~15 minutes a range of functions can be assessed. These tests should be repeated several times over the study day to assess any time profile of effects.

The advantages of determining the cognitive effects of a compound early in development are obvious and, once it becomes apparent that this is achievable, the practice will become widespread. In a rising-dose single and nine-day multiple dosing study the cognitive effects of a selective M_3 muscarinic receptor antagonist (UK76654) were assessed [8]. The compound was free of cognitive impairment with doses of up to 20 mg but was shown to possess some impairment at 40 mg. Potential target indications for an M_3 receptor antagonist are Urge Incontinence and Irritable Bowel Syndrome, both of which are typically treated by non-specific cholinergic antagonists, which also produce cognitive impairment [8]. Therefore, this study identified a dose range over which the compound should be free of cognitive impairment, giving the developers useful information at this early stage of development. In other trials of compounds designed to be free from cognitive impairing effects, such as nonsedating anxiolytics, evidence of marked cognitive impairment in Phase I studies can be a clear no-go signal for future development. In a recent first-administration-to-man study, the cognition enhancing effects of a novel antidementia compound (NS2330) were identified [9]. Therefore, the developers had proof-of-concept information by the end of the first small safety study in man. More recent work in AD patients has confirmed these effects. Properly automated tests are capable of detecting both improvements and impairments. In the development programme of the novel $5HT_{1A}$ receptor agonist, flesinoxan, cognitive function testing was included to evaluate any potential impairing effects of the compound. Instead, cognition enhancement was identified in two trials, and this was subsequently confirmed in a third study [10]. Serendipity still plays a major role in drug discovery, and the implications of these findings for the future development of the compound did not go unnoticed.

Other techniques that are available in Phase I studies include drug–drug or drug–alcohol interaction studies and a scopolamine model of AD. In one study of an early anticholinesterase, velnacrine, the compound was found to antagonize the effects of scopolamine in volunteers [11]. This potential ability to reverse cholinergic deficits in patients was subsequently confirmed in a small Phase IIA trial in 35 AD patients using the same computerized tests

as in the scopolamine study. Acute effects of antidementia drugs can also be assessed in placebo controlled cross-over trials in small groups (n = 12) of AD patients [12].

In all of the previously mentioned trials, the sensitivity of properly automated tests was largely responsible for the valuable and early information obtained in these Phase I and IIA studies. In many fields, there is little excuse for not assessing the potential presence or absence of cognitive effects before commencing large Phase II trials.

Increased targets and opportunities for cognition enhancers

The application of sensitive tests to many clinical populations is identifying cognitive impairment as a concomitant problem. Traditional medicines that effectively treat their target indications often possess cognition impairing properties as an unwanted side effect. Thus, the major symptoms of the condition are often reduced, yet the patient is still unable to function fully because of the cognition impairment. In one trial, nortriptyline – a compound that produces less cognitive impairment than the older tricyclic antidepressants – was found to reduce the cognitive impairment in elderly depressed patients compared with placebo. Interestingly, however, moclobemide, a compound with little impairing properties produced the most improvement over placebo [13].

Conditions such as schizophrenia are now becoming recognized as having cognitive impairment as potentially a core symptom of the disease. Compounds like olanzapine, which is shown using automated tests in Phase I trials to be relatively free from cognition impairment compared with traditional treatments such as haloperidol [14], have been repeatedly shown to have favourable effects on function compared with haloperidol in patients. However, this does not mean that cognitive function becomes anything near optimal in patients treated with such compounds, and there is much interest in identifying compounds that can enhance function in such patients in the hope of enabling them to fully reintegrate into society. Because of the sensitivity and utility of automated cognitive testing, these procedures should prove extremely useful in helping to identify the improvements produced by such compounds in schizophrenic patients.

Recently, epilepsy has been shown to produce marked impairments in function, such that even young patients have levels of function associated with elderly normals [15]. Treatment with compounds such as carbamazepine, which impair function in normals, also produce further cognitive impairments in patients and, although this does not lessen their clinical effectiveness in seizure control, it is obvious that drugs that could control seizures, but not further impair function, would be more desirable to patients.

The application of automated testing has identified impairments in diverse fields. Patients who undergo cardiopulmonary bypass surgery have cognitive impairments as a result [16] and cognitive dysfunction has also been identified in elderly people with untreated hypertension [17]. These are just two of many possible examples and such findings will undoubtedly arouse interest in seeking to reverse these impairments with various treatments.

Regulatory authorities are now recognizing the importance of properly conducted cognitive testing in drug development. For instance, the Efficacy Working Party of the European Medicines Evaluation Agency '…has recently specified the use of cognitive testing in a variety of neurological and psychiatric disorders. Typically the documents include reference to the use of cognitive testing in establishing the pharmacodynamic profile of the drug, as well as when monitoring for adverse events. Occasionally, guidelines also recommend that cognitive testing measures be adopted as secondary efficacy variable.' [7; p. 7.]

Herbals

Over the past decade there has been an explosion in interest in herbal substances as cognition enhancers, largely driven by the continually emerging evidence that the leaf extract from the ancient tree Ginkgo biloba is capable of improving cognitive function in a variety of populations, ranging from normal volunteers to patients with dementia. The increasing regulatory requirement to substantiate claims for herbal products has led to a range of properly controlled, randomized, double-blind clinical trials of ginkgo [e.g. 18]. Another appeal of the substance is its widespread availability in high-street chemists and its excellent safety profile. Recent work has investigated the combination of ginkgo and Panax ginseng. An initial trial indicated that this combination was capable of specifically improving the ability to retain and retrieve information from both working and secondary memory [19]. This was followed up by the largest placebo controlled, randomized, double-blind trial ever conducted in normal volunteers with a herbal compound [20]. This was reported last year and showed that in 256 middle-aged healthy volunteers, significant enhancements to memory were identified with the combination of ginkgo and ginseng over a three-month period. The benefit averaged at 7.5%, which is a substantial improvement considering that these were normal volunteers who were not showing age-related declines in memory. Importantly, automated testing was used in this work, and the ability to repeatedly test the volunteers over the study day was an important factor in identifying

these benefits. This 7.5% improvement now represents the benchmark for herbal, and other, compounds for future trials. The latest findings in this field are that single administrations of ginkgo [21], ginseng [22] and their combination [23] produce acute enhancements to various aspects of cognitive function in young student volunteers. A number of other herbal compounds are also showing promise including phosphatidylserine, sage, Brahmi and Bioglycin.

The emerging importance of attentional deficits in the dementias

The cognitive pathology of dementia has not traditionally included impairments to attention. This is evident in the DSM-IV criteria for AD [24] or, in fact, any of the dementias, where deficits to attention are not considered even as possible symptoms. This is further illustrated by the use of the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) as the major instrument in the past decade to assess the efficacy of cholinergic treatments for AD, an instrument that does not actually assess attention (i.e. 'a generally acknowledged limitation of the ADAS-Cog is that it lacks a subset for attention' [25; p. 35]). For a description of various other limitations of the ADAS the reader is referred to Harrison [7].

Paradoxically, it has long been known that demented patients, including those with AD, show impairments in tests of sustained and selective attention [26], as well as divided attention [27]. Furthermore, the sustained and selective attention deficits have been shown to be as prevalent, marked and central to the core cognitive pathology of AD, as are the more widely acknowledged impairments of episodic secondary memory [28]. For AD, in which the cognitive deficits are largely associated with cholinergic dysfunction, it is also particularly strange that attentional deficits had not been considered, as the cholinergic involvement in the control of human attention was first demonstrated in the late 1970s [29]. Furthermore, the attentional impairments in AD can be modelled in normals by blocking cholinergic transmission with scopolamine [30].

Work using automated testing has shown Huntington's Chorea to have a distinct cognitive deficit profile to AD [5]. Here, a double dissociation was found, the memory performance of the Huntington's patients being superior to the AD group, whereas the attentional deficits were more marked. Such testing has also shown vascular dementia to have an attentional component [31], which is different to that of Huntington's and AD, and is generally greater than that seen in AD. Again, there is a double dissociation in the comparison, the memory deficits in vascular dementia being smaller than those observed in AD [32].

One form of dementia in which deficits to attention are less controversial is Dementia with Lewy bodies (DLB), which has been recognized during the past decade as a common form of dementia in the elderly, accounting for 15–25% of all dementia presentations [33]. Fluctuating cognitive impairment and attentional deficits are usually accompanied by recurrent visual hallucinations and parkinsonism. Here, the attentional deficits are actually hallmarks of the dementia, and there is a strong cholinergic basis for the disease. Contrasts between DLB and AD patients have shown greater attentional impairments in DLB than in AD, but smaller deficits to episodic verbal secondary memory [32]. DLB is a disorder with more marked cholinergic deficits than AD. The first placebo controlled trial of an anticholinesterase in DLB has now been reported [33]. This was a prospective, multicentre, randomized, double-blind, placebo controlled study conducted in the UK, Spain and Italy. The treatment period was 20 weeks with a three-week post-treatment follow-up. The two primary outcome measures were a compound speed of cognitive function score derived from an automated test system and summary score from the Neuropsychiatric Inventory [34]. Analysis of the data from the 92 patients who completed the study identified a significant pattern of benefits of rivastigmine over placebo on the two main outcome criteria. Further analysis has revealed dramatic improvements to attention in this study; patients on active medication improved by an average of 22% over 12 weeks, whereas those on placebo deteriorated by 19% [4].

A commentary on this trial in *The Lancet* [35] also revealed the widening acceptance of computerized tests in dementia research: 'McKeith and coworkers show that other features, such as neuropsychological symptoms and reaction times, can be meaningful outcome measures in dementia drug trials' (p. 2025). From the above, it seems clear that there is little relevance for the ADAS-Cog for DLB, except possibly as a secondary measure to compare findings to previous trials with AD. Attention is a core feature of the disease, and assessing attention, as well as speed of access to items held in memory, is clearly essential.

At a Satellite Symposium at the *Tenth Congress of the International Psychogeriatric Association* (10 September 2001, Nice, France), Ian McKeith stressed the similarity between the cognitive impairment that develops in PD dementia and the impairment seen in DLB [36]. This, together with the similarity in the underlying neurochemical and neuroanatomical pathologies of the two conditions, would suggest that anticholinesterases would be useful treatments to apply to patients with cognitive impairment associated with PD as well as DLB. One concern here would be that motor signs would worsen but, in PD and DLB trials with

rivastigmine, patients did not experience such worsening. These findings could encourage companies to evaluate further the effects of anticholinesterases in PD, as well as DLB.

Cognitive function assessment: the future

Computerization of testing has now become accepted as a valid and practical solution to assessing cognitive function, in volunteers as well as various clinical populations, particularly of the dementias. Various computerized systems are making significant inroads into Phase I volunteer trials [1] and subsequent patient trials [25,37,38]. The superior sensitivity of properly automated tests and test systems over traditional pencil and paper testing has also emerged over recent years and has been the basis for all of the developments described in the preceding sections. Furthermore, properly automated tests allow testing to be conducted by non-specialists, greatly increasing the ease of collecting data in large, and also international multicentre, trials. As the evidence accumulates that automated procedures are more sensitive and appropriate than pencil and paper techniques, their use will enable efficacy to be established in pivotal trials with smaller numbers of patients, which has beneficial effects, not only in terms of cost [7] but also in terms of ethics as, for example, fewer patients need to be exposed to treatments before efficacy is established.

Testing is now routinely conducted using laptop computers and, soon, testing on handheld computers will become widespread. Work is also underway to develop portable devices worn as wristwatches on which various tests can be installed. Remote testing is also a highly attractive option for clinical trials. The Internet, for example, offers a great opportunity for testing; patients can log on to a website, and download and perform the tests. The data are then retrieved by the host-computer and analyzed. Such methods are just being introduced into clinical trials [e.g. 39]. Another valuable method is 'telephone testing', in which interactive voice response technology is used; the volunteer or patient calls in, answers certain questions with key presses, and then performs various tests of attention and memory. The computer presents the test stimuli over the telephone and the subjects respond by pressing certain buttons on the keypad, enabling reaction times as well as the accuracy of responding to be recorded. Two systems are currently in use in trials in the UK and North America [40,41]. One of the great advantages of both the telephone technique and the Internet technique is that the responses are collected automatically on a central database, without any requirement for the involvement of study personnel in the testing or handling of the data. Issues of potential concern with remote testing are how to verify that the subject performing the tests is the correct subject, and also how to be sure that the tests are being performed correctly and in an appropriate environment. Passwords can help verify the identity of the subject, but it will be harder to ensure that the tests are being performed appropriately. By contrast, the sample sizes available in such trials will be much larger and, as with population pharmacokinetics, this increase in sample size will almost certainly make up for the potential increased noise in the data.

Such methodology can also be used to screen patients for trials [42]. Telephone testing can be used to ensure that patients achieve the relevant inclusion–exclusion criteria. For example, if minimum levels of cognitive performance are required, patients can be excluded at an early stage if they do not fulfil the requirements. Equally, patients can be recruited if they meet certain criteria for cognitive dysfunction, for example, in trials of Mild Cognitive Impairment, or in dementia trials where certain types of impairment are sought, such as attentional dysfunction.

There is a range of interesting applications for such technology. For instance, at the University of Newcastle Dental School (Newcastle, UK), patients with dental phobia who require midazolam administration to enable routine dental work to be conducted, are participating in trials in which they phone in and perform cognitive tests at various times after having returned home. This has enabled the researchers to determine how long the various aspects of cognitive impairment persist, and also to evaluate the effectiveness of therapies to speed the rate of recovery from these impairments [43].

Conclusions

Cognitive-function assessment is now widely recognized as an important pharmacodynamic measure in drug development. Its application is becoming widespread from the first time volunteers receive novel compounds right through to pivotal studies, and thereafter in post-marketing surveillance trials. Regulatory authorities, such as the European Medicines Evaluation Agency, are mandating its use in various CNS indications, and the need to ensure that even non-CNS compounds are free from cognitive toxicity is becoming increasingly accepted. It needs to be more widely understood that it is the responsibility of psychologists to develop, implement and interpret the data from cognitive testing. Equally, broader acknowledgement is required of the multitude of advantages that properly validated automated cognitive assessment systems can bring to drug development. This review has given a range of examples of the benefits that have accrued from using automated test procedures, and recent advances in technology are making such an approach even more attractive. Properly validated automated cognitive-test systems can speed up

drug development and save money by enabling proof-of-principle evaluations to be conducted at an earlier stage of development, as well as enabling efficacy to be established in pivotal trials in smaller cohorts of patients. In the right hands, properly automated and validated cognitive test systems are hugely powerful tools for drug development.

References

1 Wesnes, K.A. (2000) The value of assessing cognitive function in drug development. *Dialog. Clin. Neurosci.* 2, 185–203
2 Walker, L.G. *et al.* (1996) The cognitive effects of recombinant interleukin-2 (rIL-2) therapy: a controlled clinical trial using computerised assessments. *Eur. J. Cancer* 32, 2275–2283
3 Walker, L.G. *et al.* (1997) The psychological and psychiatric effects of rIL-2: a controlled trial. *Psychooncology* 6, 290–301
4 Wesnes, K. *et al.* Effects of rivastigmine on cognitive function in Dementia with Lewy Bodies: a randomised placebo-controlled international study using the Cognitive Drug Research computerised assessment system. *Dement. Geriatr. Cogn. Disord.* (in press)
5 Mohr, E. *et al.* (1996) The utility of clinical trial batteries in the measurement of Alzheimer's and Huntington's dementia. *Int. Psychogeriatr.* 3, 397–411
6 Brooke, C. *et al.* (1998) The effects of intravenous morphine on cognitive function in healthy volunteers. *J. Psychopharmacol.* 12, A45
7 Harrison, J. (2001) Cognitive Testing and Drug Development. *Clin. Res. Focus* 12, 5–11
8 McEwen, J. *et al.* (1995) The cognitive effects of single and multiple doses of UK 76,654, a selective M3 muscarinic antagonist in healthy volunteers. *Eur. J. Clin. Invest.* 25, A64
9 Jones, S. *et al.* (1999) First in man cognitive effects of NS2330, a novel monoamine reuptake inhibitor, in volunteers. *J. Psychopharmacol.* 13, A26
10 van Harten, J. *et al.* (1996) No kinetic or dynamic interaction between flesinoxan and fluoxetine. *Eur. Neuropsychopharmacol.* 6, A40
11 Siegfried, K.R. (1993) The pharmacodynamics of velnacrine: Results and conclusions from clinical studies in healthy subjects and patients with Alzheimer's disease. In *The Management of Alzheimer's Disease*. (Wilcock, G.K., ed), pp. 189–201, Wrightson Biomedical Publishing
12 Templeton, L. *et al.* (1999) A double-blind, placebo-controlled trial of intravenous flumazenil in Alzheimer's disease. *Hum. Psychopharmacol.* 14, 239–245
13 Wesnes, K. *et al.* (1994) The cognitive effects of moclobemide and nortriptyline in elderly, depressed patients. Paper presented at the *Annual Meeting of the British Association for Psychopharmacology*, 10–13 July, Cambridge, UK
14 Beuzen, J-N. *et al.* (1999) A comparison of the effects of olanzapine, haloperidol and placebo on cognitive and psychomotor functions in healthy elderly volunteers. *J. Psychopharmacol.* 13, 152–158
15 Hargaden, N.J. *et al.* (2001) The therapeutic implications of idiopathic cognitive function impairments in disease: a study of a large cohort of epilepsy patients. *J. Psychopharmacol.* 15, A51
16 Fearn, S.J. *et al.* (2001) Cerebral injury during cardiopulmonary bypass: emboli impair memory. *J. Thorac. Cardiovasc. Surg.* 121, 1150–1160
17 Harrington, F. *et al.* (2000) Cognitive performance in hypertensive and normotensive older subjects. *Hypertension* 36, 1079–1082
18 Wesnes, K. *et al.* (1987) A double-blind placebo controlled trial of Tanakan in the treatment of idiopathic cognitive impairment in the elderly. *Hum. Psychopharmacol.* 2, 159–171
19 Wesnes, K. *et al.* (1997) The cognitive, subjective and physical effects of a Ginkgo biloba/Panax ginseng combination in healthy volunteers with neurasthenic complaints. *Psychopharmacol. Bull.* 33, 677–683
20 Wesnes, K.A. *et al.* (2000) The memory enhancing effects of a Ginkgo biloba–Panax ginseng combination in healthy middle aged volunteers. *Psychopharmacology* 152, 353–361
21 Kennedy, D.O. *et al.* (2000) The dose-dependent cognitive effects of acute administration of Ginkgo biloba in healthy young volunteers. *Psychopharmacology* 151, 416–423
22 Kennedy, D.O. *et al.* (2001) Dose-dependent changes in cognitive function and mood following acute administration of ginseng to healthy young volunteers. *Nutr. Neurosci.* 4, 295–310
23 Kennedy, D.O. *et al.* (2001) Differential, dose-dependent changes in cognitive performance following acute administration of Ginkgo Biloba/Panax ginseng combination to healthy young volunteers. *Nutr. Neurosci.* 4, 399–412
24 American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*. (4th edn), American Psychiatric Association
25 Ferris, S. *et al.* (1997) Objective psychometric tests in clinical trials of dementia drugs. Position paper from the International Working Group on Harmonisation of Dementia Drug Guidelines. *Alzheimer Dis. Assoc. Disord.* 11, 34–38
26 Simpson, P.M. *et al.* (1991) The cognitive drug research computerised assessment system for demented patients: a validation study. *Int. J. Geriatr. Psychiatry* 6, 95–102
27 Nebes, R.D. and Brady, C.B. (1989) Focussed and divided attention in Alzheimer's disease. *Cortex* 26, 305–315
28 Wesnes, K.A. (1996) The extent of the involvement of cholinergic deterioration in the profile of cognitive impairment seen in Alzheimer's disease. *Proc. Br. Psychol. Soc.* 4, 93
29 Wesnes, K.A. (1977) The effects of psychotropic drugs on human behaviour. *Mod. Prob. Pharmacopsychiatry* 12, 37–58
30 Wesnes, K.A. (1996) The pathology of attention of the dementias. *J. Psychopharmacol.* 10, A51
31 Walker, M.P. *et al.* (2000) Quantifying fluctuation in Dementia with Lewy Bodies, Alzheimer's disease and vascular dementia. *Neurology* 54, 1616–1625
32 Ayre, G.A. *et al.* (1997) Dementia with Lewy Bodies, Alzheimer's disease and vascular dementia show distinct patterns of cognitive impairment. *J. Psychopharmacol.* 11, A56
33 McKeith, I. *et al.* (2000) Efficacy of rivastigmine in dementia with Lewy bodies: results of a randomised placebo-controlled international study. *Lancet* 356, 2031–2036
34 Cummings, J.L. *et al.* (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44, 2308–2314
35 Cummings, J.L. (2000) Cholinesterase inhibitors: expanding applications. *Lancet* 356, 2024–2025
36 McKeith, I.G. (2001) Symptomatic Disturbances in Parkinson's Disease and Dementia with Lewy Bodies. Satellite Symposium entitled: Developments in the understanding and treatment of Alzheimer's disease and related dementias. *Tenth Congress of International Psychogeriatric Association*, 10 September, Nice, France, pp. 9–14
37 Cutler, N.R. *et al.* (1994) The use of the computerized neuropsychological test battery (CNTB) in an efficacy and safety trial of BMY 21,502 in Alzheimer's disease. *Ann. New York Acad. Sci.* 674, 332–336
38 Swainson, R. *et al.* (2001) Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. *Dement. Geriatr. Cogn. Disord.* 12, 265–260
39 McCue, P. *et al.* (2001) Self-reports of memory dysfunction in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS): A web-based study. *J. Psychopharmacol.* 15, A22
40 Mundt, J.C. *et al.* (1997) Psychological assessment via interactive voice response systems. *Behav. Res. Methods Instrum. Comput.* 29, 506–518
41 Wesnes, K.A. *et al.* (2000) The administration of the cognitive drug research computerised assessment system over the telephone: validity, utility and sensitivity. *Int. J. Neuropsychopharmacol.* 3, S364
42 Mundt, J.C. *et al.* (2001) Computer-automated dementia screening using a touch tone telephone. *Arch. Intern. Med.* 161, 2481–2487
43 Hargaden, N. (2000) Using cognitive testing over the telephone to measure the deficits due to midazolam administered to dental patients plus the reversal of these effects with flumazenil. *Proc. Br. Psychol. Soc.* 9, A88