Detecting patients with alzheimers disease suitable for drug treatment: comparison of three methods of assessment

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SUMMARY

Background. *Therapy to enhance cholinergic function in the brain is under evaluation for the treatment of alzheimers disease. Tetrahydroaminoacridine (tacrine) has recently received a product licence in the United States of America for the treatment of alzheimers disease, and the licence application in the United Kingdom will shortly be reviewed. It is therefore possible that this drug will become available for use in the UK in due course. There will then be a need for screening procedures for a large number of elderly patients to decide whether or not they have dementia and, if so, whether it is the result of alzheimers disease and is suitable for treatment with the new drug.*

Method. *A total of 246 patients aged 75 years or over in two general practices in Bristol were assessed to investigate the potential workload such screening would engender. Three different assessment schedules for the diagnosis of dementia were compared — the mini-mental state examination, the Kew test, and the abbreviated mental test score.*

Results. *None of the assessment schedules was found to be particularly onerous, with median times for administration of five, three and two minutes, respectively. A score of 23 or less on the mini-mental state examination was taken as the main cut-off point for further evaluation. Sixty six patients obtained this score — in 25 the low score reflected factors other than dementia, and 11 others declined further assessment. Of the remaining 30 patients only four had probable alzheimers disease at an appropriate level of severity for treatment, and lived with a carer who could ensure compliance and monitor side effects. Two of these patients were receiving conflicting medical treatment and a third declined therapy, leaving only one person for whom treatment could be prescribed.*

Conclusion. *It seems likely that of those medically suitable for treatment, it may not be possible to prescribe tacrine for an appreciable proportion. Nevertheless, all potential patients should be screened as the procedures involved are not onerous and at least some of those found suitable for treatment are likely to benefit from this new approach.*

Keywords: senile dementia; alzheimers disease; geriatric screening; workload; drug therapy.

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Introduction

A NUMBER of studies of cholinergic therapy for alzheimers disease have been reported.[1,2] Physostigmine and the aminoacridines, for example, tetrahydroaminoacridine (tacrine), are probably those most extensively investigated, especially tacrine, and there is increasing evidence that such treatment may be modestly effective.[3,4] It is likely that there would be considerable demand following the advent of a therapy of proven success, affecting general practitioners and their teams and the relevant hospital clinics. There would be a need for assessment, treatment where appropriate, and eventually follow up of those treated.

It was therefore decided to use the possible introduction of tacrine as a model to investigate the most practical and reliable minimum requirements for the assessment of cognitive function in elderly people, including an assessment of the time involved in conducting three simple but widely used brief testing schedules. Although it was not intended to conduct a prevalence study of dementia in the community, an attempt was made to obtain some indication of the proportion of elderly people suffering from dementia in the practices studied who had probable alzheimers disease suitable for treatment with tacrine.

The methods employed were designed to complement the screening of people aged 75 years and over, that is now a standard part of general practice. Due regard was paid to the additional work that would be created for the practice team, the side-effect profile of tacrine, and the practical aspects of administering such treatment, for example, compliance and evaluation of benefit. It was envisaged that the primary care team would be able to conduct preliminary screening, referring those apparently suitable for treatment to a hospital clinic for further evaluation, as tacrine and similar compounds have a side-effect profile that initially requires careful monitoring.[3,4]

Method

The study was conducted between April and December 1991. All patients aged 75 years or over in one practice and a one in three sample of people of this age in a second practice in Bristol were included in the study, a total of 332 patients. All patients were included whether they lived in the community or in residential or nursing homes. Each patient was sent a letter from a research nurse (D A) which included details of an appointment when the nurse proposed to visit. The purpose of the visit was explained and it was stressed that the visit was being made with the knowledge of the patient's family doctor. Those who did not respond to the appointment letter were sent a second appointment, stating that the nurse would call unless otherwise contacted. At the appointment the aim of the visit was again discussed allowing patients the opportunity to give informed consent or to withdraw at any stage throughout the visit.

Mental status testing

Three simple and practical screening schedules were employed — the mini-mental state examination,[5] the Kew test,[6-9] and the abbreviated mental test score.[10] These were administered by the research nurse, who had received training in a hospital clinic.

The mini-mental state examination was chosen as a basis for comparison with the other two schedules as it is has been extensively validated and widely accepted internationally as a preliminary screening tool in this context.[11-14] For this study a cut-off point of 23 or less was used to indicate a need for further assessment. The Kew test was chosen because of its simplicity of use and, for a short assessment schedule, the breadth of cognitive parameters assessed. The abbreviated mental test score was used as a form of this is included in the dementia pack produced by the Alzheimer's Disease Society which was sent to all general practitioners in the United Kingdom in March 1990. Each of the tests was administered in random order and questions appearing on more than one test were asked only once and marked on the other papers accordingly.

Further assessment

All patients scoring 23 or less on the mini-mental state examination were the subject of further discussion between their general practitioner, the research nurse, and an experienced geriatrician, together with scrutiny of the case notes, as a low score does not necessarily indicate cognitive impairment. Where other factors were judged to account for the low score patients were referred to the primary care team for further follow up. This included assessment of any apparent disability responsible for the low score and also further enquiry about the presence or absence of a co-existing dementia.

For patients who appeared to have dementia caused by alzheimers disease scoring 11–23 on the mini-mental state examination, and who lived with a carer so that compliance with and efficacy of therapy could be effectively monitored, the research nurse and/or general practitioner offered the opportunity for further evaluation at the memory disorders clinic in Bristol to confirm or exclude the diagnosis. The lower cut-off point of 11 was chosen because this is the level adopted in many of the clinical trials of tacrine. The clinic evaluation includes taking a history from a relative or someone else who knows the patient well where possible, a full physical examination, extended psychometric screening, appropriate investigations for treatable underlying conditions, and where necessary psychiatric assessment, in order to confirm the presence of dementia and ascertain its likely cause. Dementia was defined according to the criteria in *DSM-III-R*[15] and probable alzheimers disease on the basis of the McKhann criteria.[16] After the visit to the clinic patients with probable alzheimers disease were considered suitable for treatment with tacrine if there was no conflicting medical condition or treatment regimen.

The medical notes of all patients refusing to participate in the study were examined by their general practitioner to ascertain whether there was any evidence to suggest cognitive impairment. Although the number of patients where there was such evidence was notified to the study team, the names of the individuals concerned were not, thus maintaining confidentiality.

Analysis

Correlations were calculated by Spearman's rank correlation test using *Unistat* version IV.

The study was Approved by Frenchay District Ethics Committee.

Results

Of the 332 potential subjects, 246 (74.1%) were assessed. The remaining 86 (25.9%) comprised 29 who had died, left the area, or were untestable because of the severity of their cognitive impairment, and 57 who declined to participate in the study. The mean age of the 246 patients included in the study was 82 years (range 75–94 years) at the time of testing, and there were 157 women and 89 men (ratio 2:1). Nearly half, 45.9%, lived alone.

Of the patients screened 239 (97.2%) were able to complete all three tests, and only two people were unable to complete the mini-mental state examination.

Test duration

The quickest test to administer, measured on a stop watch, was the abbreviated mental test score which took a mean of 2.2 minutes (range 1.0–7.0 minutes). The mean for the Kew test was 3.5 minutes (range 1.5–9.0 minutes) while for the mini-mental state examination the mean time was 5.3 minutes (range 2.5–12.5 minutes). The median administration times for the abbreviated mental test score, Kew test and mini-mental state examination were 2.0, 3.0 and 5.0 minutes, respectively (rounded to the nearest half minute).

For 64 patients scoring 23 or less on the mini-mental state examination, the mean test durations for the abbreviated mental test score, Kew test and mini-mental state examination were 3.0 minutes (range 1.5–7.0 minutes), 4.5 minutes (2.0–9.0 minutes) and 6.5 minutes (2.5–12.5 minutes), respectively (only 62 of these patients completed the Kew test). The median administration times were 2.5, 4.5 and 6.0 minutes, respectively.

Correlation between tests

The correlations between the mini-mental state examination and the Kew test and the abbreviated mental test score are shown in Table 1. A significant correlation was obtained for both tests when compared with the mini-mental state examination, with a suggestion that the Kew test performed marginally better, although a difference of this magnitude is unlikely to be of relevance to clinical practice.

Sensitivity and specificity

Kew test. Of 66 patients scoring 23 or less on the mini-mental state examination, 62 were also assessed by the Kew test. A Kew score of three or more errors identified 40 of these 62 patients but also identified 21 patients who scored 24 or more on the mini-mental state examination. A score of two or more errors picked up 49 of the 62 patients and identified a further 51 false positives, while a score of one error or more identified 57 patients but also highlighted 118 false positives. The sensitivities, specificites and positive predictive values obtained for these cut-off points on the Kew test when compared with the mini-mental state examination are shown in Table 2.

Abbreviated mental test score. Of the 66 patients identified by the mini-mental state examination cut-off point, 64 had also been assessed by the abbreviated mental test score. Some of these

Table 1. Correlations between assessment schedules.

	All patients		Patients scoring ≤23 on MMSE	
	MMSE/ Kew test (n = 240)	MMSE/ AMTS (n = 241)	MMSE/ Kew test (n = 61)	MMSE/ AMTS (n = 62)
Spearman's rank correlation	−0.61	0.56	−0.79	0.73
t	−11.97	10.50	−9.75	8.19
Degrees of freedom	238	239	59	60
P	<0.01	<0.01	<0.01	<0.01

MMSE = mini-mental state examination. AMTS = abbreviated mental test score. n = number of patients for whom pairs of data are available.

Table 2. Sensitivities, specificities and positive predictive values for the Kew test and the abbreviated mental test score (AMTS) when compared with the mini-mental state examination.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Kew test (n = *241*)			
3+ errors	*64.5*	*88.3*	*65.6*
2+ errors	*79.0*	*71.5*	*49.0*
1+ error	*91.9*	*34.1*	*32.6*
AMTS (n = *243*)			
70% correct or less	*46.9*	*98.9*	*93.8*
80% correct or less	*70.3*	*87.2*	*66.2*
90% correct or less	*93.8*	*41.9*	*36.6*

n = total number of patients for whom both tests carried out.

patients were assessed on 10 items, but a proportion on only nine since one question involved the patient identifying two individuals and there were not always two people available for the patient to identify. The results are therefore expressed as a percentage rather than as an absolute count. A score of 90% correct answers or less identified 60 of the patients satisfying the mini-mental state examination cut-off point but also identified 104 false positives. The figures for scores at 80% and 70% or less on the abbreviated mental test score are 45 and 30 patients correctly identified, and 23 and two false positives, respectively (Table 2).

Patients with dementia and suitability for treatment

Of the 66 patients scoring 23 or less on the mini-mental state examination 25 were not believed to be suffering from dementia and their low scores were attributed to physical/psychiatric conditions. Two patients died prior to further assessment. Eleven patients refused to undergo further assessment, but neither discussion with their general practitioner nor examination of the medical notes yielded any evidence for dementia. Seven patients did not have a carer, and so would not have been suitable for treatment with tacrine, even if they had alzheimers disease of an appropriate degree of severity. All 43 were referred to their general practitioner for further follow up.

Ten patients had scores on the mini-mental state examination of 10 of less and were therefore considered to be too severely demented for treatment. Three had multi-infarct dementia and four were diagnosed as having age-associated memory impairment, that is memory loss affecting day to day life but in the absence of other impairment of mental ability such that the individual did not fulfil the criteria for dementia. This left four people with alzheimers disease who had dementia at an appropriate level of severity and a carer and they were referred to the memory disorders clinic for further evaluation. Two of these patients were taking conflicting medical therapy and after discussion with the patients and their carers, one patient declined treatment, leaving only one person who was suitable for and willing to commence a trial of tacrine.

Discussion

It is clear from the result of this study that none of the three assessment schedules chosen is particularly onerous, as all can be completed within a few minutes in the majority of cases. Of the three, the mini-mental state examination is favoured because of its wide usage, the knowledge of its limitations in different settings,[11-14] and its incorporation in other well accepted cognitive assessment procedures such as the Cambridge examination for mental disorders in the elderly (CAMDEX)[17] and the Medical Research Council guidelines for minimum data collection in studies of alzheimers disease.[18] The mini-mental state examination and the Kew test attempt to cover a wider spectrum of cognitive parameters than does the abbreviated mental test score. This study has shown that the abbreviated mental test score does not correlate quite as well with the mini-mental state examination as does the Kew test, and it may well be that the community is not the best context in which to use the abbreviated mental test score.[19] The Kew test is more affected by physical disability than the other two tests and there are no studies in the literature relating the cut-off point to the context in which it is used.

There is considerable debate about the appropriate cut-off points on the mini-mental state examination for identifying mild to severe dementia in a community sample. O'Connor and colleagues suggested that a cut-off point of 23/24 may be inappropriate for community studies in the United Kingdom,[20] while Clarke and colleagues found this cut-off point to be the most satisfactory in their more recent study.[14] Other screening instruments have been suggested as suitable in this context, including the information/orientation sub-test of the Clifton assessment scale.[14,21] Whichever method is adopted it is important to appreciate the need to interpret the cut-off point in relation to the social and demographic qualities of the population being studied, and not to use such relatively crude scales for diagnostic purposes, but rather to indicate patients who require more detailed assessment and investigation.

It may prove beneficial to include an assessment schedule in the annual health check for patients aged 75 years and over. This would allow for baseline scores to be recorded, would highlight change at subsequent assessments and as a routine annual check would probably be less threatening to the patient than a one-off unscheduled visit by an independent nurse. Previous assessment would also be helpful if a patient presented having been made aware of dementia by reports in the media. Failure to identify a patient with borderline dementia correctly in the context of routine general practice screening is likely to be readdressed at the subsequent assessment as the disease progresses. Longitudinal evaluation will always be superior to cross-sectional evaluation, and in this study patients with dementia may well have been missed and specifically some who might have been suitable for treatment with tacrine. However, it was not intended to undertake a prevalence survey but rather to obtain an approximate indication of the size of the workload engendered by such assessments in the context described. Nevertheless, even if the margin of error in this sample is several hundred per cent, there would still be a relatively small number of patients who were suitable and willing to take a drug such as tacrine. For other drugs with a less problematic side-effect profile the number of patients may be higher, but the results show how careful the pharmaceutical industry and health service planners must be when projecting the size of the population likely to take up a treatment of this type.

In summary, if carefully managed the increase in workload resulting from the licensing of a treatment for alzheimers disease is likely to be containable. If a more structured approach is undertaken, with meaningful assessment of cognitive function as part of the programmed screening of the population aged 75 years and over, the demands made upon the National Health Service should be even more manageable.

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