Review Article

Critical review of clinical trials in senile dementia – II*

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Dopaminergic substances

The role of dopamine in behavioural arousal and the frequent occurrence of dementia in patients with Parkinson's disease provide the rationale for the use of these substances in dementia, although dopamine levels in the caudate nucleus and substantia nigra are not depressed in primary degenerative dementia (PDD)⁵⁶.

L-Dopa has yielded contradictory results.⁶ Half of the trials reported an improvement in behaviour, but sometimes at the cost of impairment of memory, while the remainder found the treatment ineffective. The first studies were carried out in parkinsonian patients and showed an improvement in cognitive performance,^{57,58} but subsequent trials failed to confirm this effect.⁵⁹ In a crossover trial in 120 patients suffering from PDD, Schneck *et al.*⁶⁰ found that the patients responding to L-dopa showed an improvement in psychomotor function and mood, whereas patients responding to choline showed some improvement in memory functions.

A few studies have been carried out with amantadine either in elderly deteriorated patients⁶¹ or in elderly patients suffering from impairment of memory.⁶² The efficacy of amantadine was evaluated, using a battery of tests, in a small number of patients who did not meet the criteria of senile dementia. Thus, despite the good results reported, no assessment can be made of the drug's effectiveness in this disease.

Nicrosini & Pasotti⁶³ compared piribedil with Codergocrine mesylate in 30 patients suffering from 'cerebral arteriosclerosis', with favourable results and few side effects. Other trials on larger numbers of patients whose clinical status was not much better defined, concluded that piribedil is partially effective.^{64,65}

In an open trial bromocriptine was reported to

afford a parallel improvement in the electroencephalogram and the motor and memory components of the dementia syndrome.⁶⁶ These clinical findings are at variance with those obtained in two previous controlled trials which produced negative results despite administration of high dosages⁶⁷ and regardless of the fact that the treatment reduced blood prolactin levels.⁶⁸ In the latter study the period of observation was shorter – 4 weeks instead of 12 in the other trials. Gottfries⁶⁹ reported that some patients with PDD became confused after treatment with bromocriptine and lisuride, another dopaminergic agonist.

Neuropeptides

Clinical trials of ACTH, vasopressin and their derivatives were carried out in view of the positive effects of these substances on learning and memory in laboratory animals. After approximately 10 years of clinical research, it remains very doubtful whether these compounds are of value for the treatment of PDD.

Two ACTH derivatives – ACTH 4–10 and ACTH 4–9 (Organon 2766) – which are devoid of any stimulant effect on the adrenal glands have been the subject of clinical trials. Both compounds were very well tolerated, but were not found to have an appreciable effect in controlled trials,^{70–74} despite the fact that they exerted some positive effects on cognition in normal young subjects and elderly volunteers.^{75–77}

Vasopressin: trials have been carried out with lysine vasopressin (LVP), desglycinamide arginine vasopressin (DGA VP) and desmoro-des-arginine vasopressin (DDA VP). LVP may improve memory performance in normal elderly subjects,⁷⁸ and an open study suggests that this may hold also for patients with PDD,⁷⁹ whereas conflicting results have been obtained in patients with amnesia of organic origin.⁸⁰ Few of the controlled clinical trials related to dementia proper, and the results obtained in amnesia (due to Korsak-

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off's syndrome or post-traumatic) are anecdotal and contradictory.⁶

Cholinergic substances and precursors

Demonstration that in the brains of patients with Alzheimer's disease the cholinergic neurones of the hippocampus and frontal cortex have degenerated,^{81,82} and that choline-acetyl-transferase levels are depressed⁸³⁻⁸⁵ prompted a number of clinical trials of the acetylcholine precursors choline and lecithin. As usual these trials ran in two phases: first a series of open or small-scale trials, some of which produced moderate improvement in memory⁸⁶⁻⁹⁰ while others yielded negative results.⁹¹⁻⁹⁴ In a second phase the compounds were the subject of controlled clinical trials which were nearly all negative.⁹⁵⁻⁹⁷ Another cholinergic precursor, deanol, was investigated in a few trials and found to have no effect on any of the symptoms of dementia.^{6,98}

As a parallel development, physostigmine was tested because of its indirect cholinomimetic action: apart from modest and usually transient improvement in memory,⁹⁹⁻¹⁰⁴ no lasting effect was observed on the intellectual performance and the day-to-day behaviour of patients with Alzheimer's disease. This applied whether the drug was given alone or together with lecithin.^{105,106} Furthermore, the drug has a number of practical drawbacks: it is poorly absorbed from the gut, has a short plasma half-life and, with a bell-shaped dose-effect curve, it produces appreciable side effects, as the toxic blood level is close to the therapeutic one.¹⁰⁷

The results obtained with other cholinomimetic agents such as 4-aminopyridine, tetrahydroamino-acridine (THA) and arecoline, were hardly more convincing, in view of the small numbers of patients studied and the short periods of observation:¹⁰⁸⁻¹¹⁰ the only regularly observed effect was a modest, if inconsistent and frequently transient, improvement of memory*. Another postsynaptic muscarinic agonist, RS 86, afforded an improvement in clinical status and in performance in some psychometric tests in two controlled trials in a small number of patients with probable Alzheimer's disease.¹¹¹

Combination of lecithin with the anticholinesterase agent THA led to only moderate improvement of memory in deteriorated elderly patients.¹¹² Lecithin combined with physostigmine was tested in several

trials, sometimes affording an improvement of memory which was not, on the whole, of clinical significance.^{106,113,114} More recently a trial of lecithin administered at high doses for long periods to patients with Alzheimer's disease¹¹⁵ failed to reveal any overall improvement although the authors suggest that the treatment was beneficial in some patients with intermediately high plasma levels.

In agreement with Crook¹¹⁶ it may be concluded that acetylcholine precursors are not really effective in PDD, although some minimal improvement has been observed in patients treated with a combination of lecithin and piracetam, and with physostigmine, arecoline or THA. In our view these trials of the cholinomimetics show that, although it may be possible to improve memory in normal subjects with pharmacological agents given under experimental conditions, the same drugs are relatively ineffective in patients suffering from clinically well-defined dementia. This may be due to the fact that an alteration in the neurochemical target systems is the cause both of the symptoms (here memory impairment) and of the resistance of these symptoms to treatment. Nevertheless, this particular therapeutic approach is still an interesting one, and it is likely that more effective and better tolerated drugs – cholinesterase inhibitors and direct agonists – will soon be developed and submitted to clinical testing.

Psychotropic agents: neuroleptics, minor tranquillizers, antidepressants

The use of psychotropic agents in senile dementia is based on the hypothesis that anxiety and depression, possibly engendered by the patient's awareness of the deterioration in his condition, and the agitation resulting from mental confusion are factors which contribute to the patient's loss of independence and to the intolerance he arouses in those around him. Drugs of this type have not been investigated in many trials since the 1970s.

Neuroleptics have fallen into disfavour, at least for the early stages of the disease, because in many patients they can precipitate confusion or exacerbate dementia.¹¹⁷ Trials have been carried out mainly with chlorpromazine, trifluoperazine, haloperidol, thioridazine, penfluridol, butyrylperazine and thiothixene.¹¹⁸ The positive trials reported an improvement in behaviour and agitation, whereas other studies indicated that at moderate doses neuroleptics are either without effect on behavioural disturbances or may, indeed, exacerbate the mental disturbances. Nevertheless, these drugs are useful when behavioural symptoms become intolerable for those close to the patients, and they make it possible to avoid or postpone admission to an institution.

*Since this paper was accepted for publication, another study by Summers *et al.* (*New England Journal of Medicine*, 1986, **315**: 1241-1245) showed a clinically meaningful effect of THA administered orally in 17 patients with moderate to severe Alzheimer's disease. This benefit lasted for a mean of 12.6 months in 12 patients given THA in the long term, with no, or only minor, side effects.

The prevailing opinion is that, on the whole, neuroleptics should be avoided in early dementia and should be used cautiously when serious behavioural troubles, especially when associated with paranoid states, make sedative treatment necessary.⁵

Minor tranquillizers are widely used, although some of them may induce or exacerbate confusional states.¹¹⁹ In a detailed review of tranquillizer use in psychogeriatrics,⁵ four trials in elderly patients suffering mainly from anxiety and/or agitation suggested that diazepam had a beneficial effect on the signs of anxiety and on insomnia. However, side effects, notably drowsiness and/or confusion, were increasingly troublesome the greater the age of the patients. In other trials oxazepam gave comparable results, but had no effect on agitation.

These findings tally with general clinical experience: the minor tranquillizers are often preferred to neuroleptics for treatment of anxiety and agitation in deteriorated elderly patients.¹²⁰ However, if the patient's condition worsens and moderate doses no longer suffice, it may be preferable to switch to neuroleptics,¹²¹ thereby avoiding high doses of minor tranquillizers which might induce hypotension, ataxia or somnolence.

Antidepressants are used with caution in senile dementia since they may induce confusion, but they are often prescribed on the grounds that depressive 'pseudodementia'¹²² might be responsible wholly or in part for the signs and symptoms of mental deterioration in the elderly. The earlier literature⁵ does not suggest that tricyclic antidepressants are particularly effective in dementia, except in frank depressive states. On the other hand, these studies also report that side effects of antidepressants in elderly patients are not excessive. A study of Gerner *et al.*¹²³ compared trazodone with imipramine in the treatment of depression in elderly patients and concluded that trazodone was better tolerated but that both drugs were without effect on the cognitive deficits. A controlled trial of minaprine¹²⁴ in senile dementia (PDD and MID) indicated that cognitive function improved roughly in parallel with the improvement in the symptoms of depression, the response being better in vascular dementia than in PDD. There were few side effects. Alaproclate, which inhibits 5-hydroxytryptamine reuptake, appeared promising in a pilot study,¹²⁵ but from a controlled study in 40 very old patients suffering from PDD, it was concluded that overall the drug was ineffective, despite some positive effect on intellectual function. Furthermore, any improvement was bought at the price of fairly severe side effects.¹²⁶

Naloxone

One of the latecomers in the treatment of senile

dementia, naloxone, has already been tested without much success in a number of central nervous system disorders. This drug went the way of numerous predecessors: after hopes had initially been raised by the findings obtained in an open study in PDD,¹²⁷ its effectiveness was soon contested.¹²⁸ A first controlled trial confirmed that the drug had a beneficial effect,¹²⁹ but subsequent studies called these results into question.¹³⁰ In view of the fact that the rationale behind the use of the drug rests on a flimsy physiological basis, it is likely that, after a few further trials or perhaps even without them, naloxone will join that ever-growing band of drugs which have been tried for the treatment of PDD and abandoned.

Conclusion

Although this review does not appear very encouraging, we are of the opinion that this long series of clinical trials albeit partially or wholly unfruitful, should not be seen in a sceptical or nihilistic light. On the positive side we have the fact that some useless or potentially dangerous drugs have been identified, from which present and future patients have been spared. In addition, more pragmatic and more effective methods of clinical testing have been developed, and drug trials in psychogeriatrics have now reached an acceptable standard.

It is clear that drugs will have to continue to be tested empirically, in view of the urgent need to find a treatment which is at least partially effective. Some compounds mentioned in this paper remain as possible candidates for therapy, although they do not afford either spectacular or really consistent improvement. Moreover, it is possible that selection of more homogeneous subgroups among the whole population of PDD patients^{131,132} might provide an opportunity to test the effects of one or other compound with greater specificity. Furthermore, the gravity of the medium-term prognosis in these patients^{133,134} has to be taken into account in designing future trials, which should last longer than the usual 6–12 weeks.

It would seem, nevertheless, that the best way to find a real solution to the problem posed by primary degenerative dementia would be to succeed in identifying a causative agent, or aetiological factor(s), amenable to control. This would permit prevention or specific treatment of the disease. Until that day arrives, we should concentrate our efforts on three approaches: firstly development of substitution therapy, in which we may take encouragement from the example of what has been achieved in Parkinson's disease, secondly empirical treatment wherever there is a reasonable chance that it might be of some usefulness and thirdly symptomatic treatment of the secondary psychiatric disturbances.

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