

## REVIEW ARTICLE

# Cognitive Enhancing Agents: Current Status in the Treatment of Alzheimer's Disease

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**ABSTRACT:** Extensive recent literature on drugs used to enhance cognitive functioning, reflects the growing social problem of dementia. Many clinical trials have been undertaken with variable success. In most cases the disorder studied has been Alzheimer's disease. The pharmacological approach has been designed to rectify the presumed pathophysiological processes characteristic of the condition. Agents tested include cerebral vasodilators, cerebral metabolic enhancers, nootropics, psychostimulants, neuropeptides and neurotransmitters with a special emphasis on drugs used to enhance cholinergic function. Ethical and practical issues concerning clinical drug trials in dementia will be discussed.

**RÉSUMÉ:** *Stimulation cognitive médicamenteuse: état de la question dans le traitement de la maladie d'Alzheimer* La multiplicité des publications récentes sur les médicaments utilisés pour stimuler le fonctionnement cognitif est le reflet du problème social sans cesse croissant de la démence. Plusieurs essais cliniques ont été tentés avec des résultats variables. Dans la plupart des cas, la maladie étudiée était la maladie d'Alzheimer. L'approche pharmacologique a été conçue pour corriger les processus physiopathologiques caractéristiques de la maladie. Les agents étudiés incluent des vasodilatateurs cérébraux, des stimulants métaboliques cérébraux, des agents nootropes, des agents neurotropes, des psychostimulants, des neuropeptides et des neurotransmetteurs, avec une emphase particulière sur les médicaments utilisés pour stimuler la fonction cholinergique. Nous discutons des considérations éthiques et pratiques touchant les essais thérapeutiques dans la démence.

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Because of the growing elderly population, many with forgetfulness and dementia, there is considerable interest and support for neuropharmacology involving cognitive enhancing agents (Table 1). Although there are many etiologies of dementia, the most studied area has been that of Alzheimer's disease.

As the underlying pathophysiology of this disorder becomes clearer, more "rational" approaches to the pharmacology of this disorder are being discovered and tested. Interest is mainly directed towards improving the brain function or delaying the cognitive deterioration associated with Alzheimer's disease, although other dementing illnesses (such as alcoholic dementia) many benefit from these therapeutic strategies.

Some contend that the underlying pathophysiology is diverse and not amenable to pharmacological manipulation.<sup>1</sup> Most categories of drugs, however, have been developed with some underlying pathophysiology in mind. The cerebral vasodilators were developed when arteriosclerotic dementia was a popular concept.<sup>2</sup> Neuropeptide substrates for memory were based mainly on animal models of memory loss. But, there is some

evidence that the extinction of conditioned avoidance response employed in these studies is not analogous to human memory loss.<sup>3</sup> General metabolic enhancers were developed to improve glucose utilization. Subsequently, PET scanning has proven that glucose utilization is impaired in Alzheimer's disease.<sup>4</sup>

The strategy with the soundest pharmacologic basis involves cholinergic augmentation. Early studies with anticholinergics showed that these agents produced memory dysfunction<sup>5</sup> and that cholinergic agonists corrected this.<sup>6</sup> Further strength was added to the cholinergic hypothesis of Alzheimer's disease, with the discovery of significant cell loss in the basal forebrain.<sup>7</sup> From these cells extend, cortical cholinergic projections. The several methods of augmenting acetylcholine which have been applied pharmacologically will be discussed.

## Cerebral Vasodilators

The premise upon which these agents were developed, was that aging and dementia were forms of "vascular insufficiency". It was felt that increased cerebral blood flow would improve cognitive functioning, but this hypothesis is no longer valid.<sup>2</sup>

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**Table 1: Pharmacological Agents Used to Treat Dementia**

| CATEGORY                            | AGENTS                                     | BENEFIT                            | REFERENCE      |    |
|-------------------------------------|--|------------------------------------|----------------|----|
| Cerebral Vasodilators               | Papaverine                                 | none                               | 8              |    |
|                                     | Cyclandelate                               | none                               | 8, 9           |    |
|                                     | Isoxsuprine                                | none                               | 2, 8           |    |
|                                     | Vincamine                                  | ?                                  | 2              |    |
|                                     | Hydergine                                  | Mood                               | 10             |    |
| Cerebral Metabolic Enhancers        | Nafronyl                                   | Unclear                            | 8              |    |
|                                     | Centrophenoxine                            | none                               | 13             |    |
|                                     | Pyriethoxine                               | ?                                  | 13             |    |
|                                     | Meclofenoxate                              | none                               | 10             |    |
|                                     | Pyritinol                                  | ?                                  | 10             |    |
| Nootropics                          | Piracetam                                  | Probably none alone                | 11, 17, 18, 19 |    |
|                                     | Pramiracetam                               | none                               | 25             |    |
|                                     | Aniracetam                                 | none                               | 29             |    |
|                                     | Oxiracetam                                 | ?                                  | 33, 34         |    |
|                                     | Suloctidil                                 | none                               | 36             |    |
| Psychostimulants                    | Methylphenidate                            | Probably none                      | 37, 38         |    |
|                                     | Amphetamines                               | none                               | 10             |    |
|                                     | Pipradol                                   | none                               | 39             |    |
|                                     | Pentylenetetrazol                          | Probably none                      | 10             |    |
|                                     | Vasopressin                                | ?                                  | 42-50          |    |
| Neuropeptides                       | ACTH                                       | ?                                  | 11             |    |
|                                     | Naloxone                                   | unclear                            | 52-56          |    |
|                                     | Naltrexone                                 | unclear                            | 57, 58         |    |
|                                     | CCK  | ?                                  | 59             |    |
|                                     | Somatostatin                               | ?                                  | 60             |    |
|                                     | Neurotransmitters                          | Levodopa                           | none           | 63 |
|                                     |  | Memantine                          | none           | 64 |
| THIP (GABA agonist)                 |  | none                               | 65             |    |
| Tryptophan (serotonin precursor)    |  | none                               | 66             |    |
| Alaproclate (serotonin potentiator) |  | none                               | 67             |    |
| Zimeldine (serotonin potentiator)   |  | none                               | 68             |    |
| Choline                             |  | none                               | 70, 71         |    |
| Lecithin                            |  | none                               | 70, 71         |    |
| Physostigmine                       |  | some                               | 75-78          |    |
| Tetrahydroaminoacridine             |  | Initiative=yes, Cognition=possibly | 79, 80         |    |
| Arecoline                           |  | ?                                  | 75             |    |
| RS-86                               |  | Probably none                      | 86, 87         |    |
| Bethanecol                          |  | Unknown                            | 88             |    |
| Pilocarpine                         |  | none                               | 72             |    |
| 4-Aminopyridine                     |  | some                               | 89             |    |
| Neurotransmitters Combinations      | Intracranial Bethanecol                    | Probably none                      | 90, 91         |    |
|                                     | Piracetam and Choline                      | some patients                      | 19             |    |
| Miscellaneous                       | Piracetam and Lecithin                     | none                               | 73             |    |
|                                     | Lecithin and Tetrahydroaminoacridine (THA) | possibly                           | 79, 80         |    |
|                                     | Lecithin and Physostigmine                 | ?                                  | 74             |    |
| Miscellaneous                       | Gerovital - H3                             | none                               | 11             |    |
|                                     | Hyperbaric oxygen                          | none                               | 11             |    |

The vasodilators can be divided into direct and indirect acting agents. The former act primarily as vasodilators and the latter influence cerebral blood supply by improving neuronal metabolism.<sup>3</sup> The direct acting vasodilators include papaverine, cyclandelate, nafronyl, isoxsuprine and vincamine. The second group includes hydergine and meclofenoxate.

No useful clinical effect has been found with papaverine,<sup>8</sup> cyclandelate,<sup>8,9</sup> isoxsuprine,<sup>2,8</sup> and vincamine,<sup>2</sup> in Alzheimer's disease. Hydergine, a combination of three hydrogenated alkaloids of ergot is best known to neurologists. Although improvement in social function has been demonstrated in many studies,<sup>10</sup> no clear cut memory, cognitive or objective change has been consistently found.<sup>11,12</sup>

### Cerebral Metabolic Enhancers

This is a poorly understood class of drugs. There is considerable overlap between these agents and the cerebral vasodilators

and nootropics. The rationale behind metabolic enhancement is improvement of brain energy through carbohydrate metabolism and ATP synthesis.<sup>13</sup>

Nafronyl has been shown to increase brain utilization of glucose and oxygen in rats and mice.<sup>13</sup> Although some studies have demonstrated improvement in neuropsychological tests and behavioural scores, they cannot be compared and therefore conclusions cannot be drawn.<sup>10,13</sup>

Centrophenoxine<sup>13</sup> and meclofenoxate<sup>10</sup> are not efficacious in dementia. Pyriethoxine<sup>13</sup> and pyritinol<sup>14</sup> have not been thoroughly studied.

### Nootropics

The term nootropic (noos mind tropein forward) was coined by Cornelia Giurgea in 1972.<sup>15</sup> These agents were developed to enhance cognitive function without being sedatives, analgesics or neuroleptics.<sup>16</sup> The mechanism of action is not felt to be

through any neurotransmitter system. In dementing illness, in which the underlying pathophysiology may be diverse, a non-specific mental or cognitive enhancer is attractive.

Piracetam is the prototype for this entire group of drugs. It has been shown to stimulate the conversion of ADP to ATP under normal and hypoxic conditions.<sup>13</sup> The use of piracetam in dementia has resulted in variable outcomes. Although some effect has been noted at lower doses (2.4 gm/day)<sup>17,18</sup> with less or no effect at higher doses (4.8 gm<sup>11,17</sup> and 7.2 gm/day<sup>19</sup>) there are some difficulties with the studies. The populations were poorly defined and not clearly consisting of Alzheimer's disease patients.<sup>17,18</sup> No standard cognitive instruments were used for assessment in one trial.<sup>18</sup>

The clinical results with piracetam alone have not been dramatic but there is a better effect with piracetam and cholinergic agents combined. One animal study demonstrated a synergistic effect on memory retention with choline (a cholinergic precursor) and piracetam.<sup>20</sup> Moderately impaired Alzheimer patients showed a better response with piracetam and choline in one trial, than with either agent alone.<sup>19</sup> This response is directly correlated with red-cell choline levels, but was only present in four of fifteen patients studied. One group of investigators has demonstrated that piracetam diminishes hippocampal acetylcholine levels in rats and they propose that this is through increased acetylcholine release.<sup>22</sup> Therefore, it may be that piracetam's pharmacology is not as nonspecific as was originally speculated. Part of its mechanism of action may be through activation of the cholinergic system and this may be why the combination of the two agents showed synergism.

Pramiracetam is an analog of piracetam which has been shown to improve memory in animal models.<sup>23</sup> Its mechanism of action is not clear, but it increases the rate of high affinity choline uptake in rat hippocampus.<sup>24</sup> This is an indirect effect as it cannot be replicated by direct application of pramiracetam onto hippocampal slices. Therefore, it has been postulated that pramiracetam causes increased release of acetylcholine from its terminals.<sup>24</sup> The increased uptake of choline occurs only within a certain therapeutic window, like that seen with piracetam.<sup>11</sup> In the sole clinical trial of this agent, it was found to be well tolerated and had some positive effect on motivation and mood. No significant change was found in the well designed cognitive assessment battery.<sup>25</sup>

Another nootropic agent, aniracetam has been shown to enhance memory in animal models.<sup>26,27,28</sup> Its pharmacological action is not known. In one recently reported clinical trial, it was found not to have any beneficial effect as compared with placebo in patients with Alzheimer's disease.<sup>29</sup>

Oxiracetam (CGP 21690E) is a hydroxyderivative of piracetam. Preclinical studies have shown that oxiracetam reduces amnesia and facilitates learning in aged animals.<sup>31,32</sup> An early study on "organic brain syndrome" showed a superior effect compared with piracetam on memory function.<sup>33</sup> Two recent phase II clinical trials (first studies in intended population) demonstrated significant improvement in some psychometric tests compared with placebo in a population of mixed dementias.<sup>33,34</sup> In addition, a standard quality of life scale improved significantly in one study.<sup>34</sup> The main criticism of these two studies is the inclusion of patients with multi-infarct dementia and the use of some unvalidated psychometric tests.

The mechanism of action is unclear, but as with the other nootropics it was felt to be a nonspecific metabolic enhancer. However, there are recent reports that it stimulates high affinity choline uptake in the hippocampus<sup>35</sup> and prevents scopolamine-induced short term amnesia in rats and mice.<sup>35</sup> Although the intention of the development of the nootropics was to produce nonspecific metabolic enhancers, it appears that their activity may be through cholinergic augmentation.

The metabolic enhancer suloctidil may be classified as a nootropic until more is known about its pharmacology. In one placebo controlled trial which only looked at multi-infarct dementia, some improvement was reported with suloctidil.<sup>36</sup> This difference was demonstrated only in the clinical global impression scale, and the details of this scale are not provided. The memory tests were unchanged. The electroencephalogram showed a frequency shift (to higher frequencies) in the drug treated group. The computerized electroencephalogram has not yet proven useful in clinical drug trials.

### Psychostimulants

There is declining speed of performance associated with aging. Direct stimulation of the CNS with psychostimulants might facilitate performance and cognitive functioning.<sup>37</sup> This is the basis for the use of psychostimulants which include methylphenidate, amphetamines, pipradol, pentylenetetrazol and magnesium pemoline.

Kaplitz and others<sup>37</sup> showed improvement in a geriatric population using methylphenidate 20 mg compared with placebo controls. This was demonstrated on a mental status checklist and a nurses observation scale (NOSIE). Crook and others, a few years later in a crossover design, showed that 10 mg and 30 mg of methylphenidate has no effect on psychological test performance.<sup>38</sup>

Pentylenetetrazol (metrazol) has been widely tested in the geriatric population. In seven of seventeen controlled studies there was some favourable response to pentylenetetrazol. Overall the extensive literature on this agent is unfavourable.<sup>10</sup>

Dextroamphetamine produced paradoxical drowsiness.<sup>10</sup> Pipradol (adrenergic agonist) showed some benefit in geriatric in-patients at 3 weeks but not at 9 weeks, on the nurses observation scale for inpatient evaluations (NOSIE) and symptom rating scale.<sup>39</sup> Magnesium pemoline was not found to be any better than placebo in one controlled study.<sup>40</sup>

### Neuropeptides

There is impressive evidence that vasopressin plays a role in memory in animal models.<sup>41,42</sup> Most of this work has been elegantly performed by De Wied and colleagues.<sup>41</sup> Avoidance behaviour in rats will ultimately extinguish. Vasopressin given at any time during this learning process will delay extinction. There are similar findings with rats which have had their posterior pituitaries removed and with Brattleboro rats (hereditary diabetes insipidus). On the basis of this animal work, clinical trials have been undertaken using lysine vasopressin<sup>42,43</sup> and analogs, desmopressin (DDAVP)<sup>44,45</sup> and DGAVP.<sup>46</sup> There are clinical reports of memory improvement in elderly normal subjects<sup>47</sup> and amnesic patients treated with lysine vasopressin.<sup>48</sup> One trial with Alzheimer's patients exclusively yielded negative results.<sup>43</sup> Severe Korsakoff-type amnestics similarly did not improve.<sup>49</sup> It is postulated that a critical level of dysfunction is reached, beyond which improvement is not possible.<sup>43,46</sup> The

clinical trials with DGAVP<sup>50</sup> and desmopressin (DDAVP)<sup>44</sup> are too preliminary to be conclusive. Some argue that the extinction of conditioned avoidance response is not a good model for human memory dysfunction and that vasopressin has not been shown to be deficient in Alzheimer's disease.<sup>3</sup>

Another peptide which has been shown to play a role in animal models of memory is ACTH.<sup>51</sup> ACTH<sup>4-9</sup> and ACTH<sup>4-10</sup> have been administered to elderly normal people and cognitively impaired patients. Memory and attention are not significantly affected, but mood and anxiety were improved.<sup>11</sup>

Endogenous opioid systems may modulate memory, although the mechanism by which this is accomplished is not clear.<sup>52</sup> Intravenous naloxone was compared with placebo in a pilot study of 7 patients with Alzheimer's disease. Naloxone treated subjects showed significant improvement on most of the psychometric tests.<sup>52,53</sup> But three subsequent trials with intravenous naloxone at various doses were negative, casting doubt on the efficacy of this agent.<sup>54,55,56</sup>

Two clinical trials with naltrexone, a longer acting Opiate antagonist were negative.<sup>57,58</sup> The protocols were dissimilar, one involving multiple single variable doses<sup>57</sup> and the other a daily dose schedule with a crossover design.<sup>58</sup> In addition, the crossover study<sup>58</sup> employed active compound for only one week, nor were psychological test batteries comparable in these two studies. The short half life of naloxone and the short duration of the naltrexone trials suggests that neither agent has been adequately utilized.

No improvement in cognitive functioning was found in patients with Alzheimer's disease in the sole clinical trial of CCK.<sup>59</sup>

An analogue of somatostatin was evaluated on ten patients with no improvement seen in memory testing.<sup>60</sup> There is some interest in this compound as somatostatin is reduced in post mortem brain tissue from patients with Alzheimer's disease.<sup>61</sup>

### Neurotransmitters

Adrenergic,<sup>62</sup> dopaminergic<sup>63,64</sup> gabaminergic<sup>65</sup> and serotonergic<sup>66,67,68</sup> therapies have generated only modest interest compared with the vast, expanding literature on acetylcholine. The basis for this interest is the cholinergic hypothesis of dementia which asserts that loss of cholinergic neurons in the basal forebrain is responsible for the memory loss associated with Alzheimer's disease. It is not the intent of this article to review all the evidence behind the cholinergic hypothesis. It has been amply summarized elsewhere.<sup>69</sup>

The cholinergic agents which have been studied to date are classified in Table 2. One can divide the agents into 1) presynaptic or acetylcholine precursor therapy, 2) cholinergic or synaptic enhancers (acetylcholinesterase inhibitors) and 3) post-synaptic receptor agonists.

### Acetylcholine Precursors

Extensive testing of the presynaptic agents has not revealed any therapeutic benefit.<sup>70,71</sup> This may be due to extensive cholinergic cell loss in Alzheimer's disease. The surviving cholinergic cells may not be able to compensate even when deluged with precursor.<sup>72</sup> Alone these agents have not been effective, but there has been some interest in combining them with piracetam<sup>19,73</sup> and anticholinesterase inhibitors.<sup>74</sup> Piracetam and choline were combined in one clinical trial with positive results

**Table 2: Cholinergic Agents**

| <b>Acetylcholine Precursors</b>      |  |
|--------------------------------------|--|
| Lecithin (Phosphatidylcholine)       |  |
| Choline Chloride                     |  |
| <b>Synaptic Enhancers</b>            |  |
| Physostigmine                        |  |
| Tetrahydro aminoacridine             |  |
| <b>Post Synaptic Agonists</b>        |  |
| Arecoline                            |  |
| RS - 86                              |  |
| Bethanechol                          |  |
| <b>Others</b>                        |  |
| 4-Aminopyridine                      |  |
| Intracranial Infusion of Bethanechol |  |

in four of fifteen patients studied.<sup>19</sup> Treatment responders tended to have higher red-cell choline levels.<sup>21</sup> Piracetam plus lecithin, failed to affect cognition in 18 patients.<sup>73</sup> In one trial, lecithin combined with physostigmine improved memory measured by a complicated task.<sup>74</sup> Consistent benefit was found in both the open and crossover stages of this study. Other cognitive functions were not assessed.

### Synaptic Enhancers

Cholinesterase inhibitors increase acetylcholine by preventing its breakdown. Physostigmine crosses the blood brain barrier and has been the most thoroughly studied of this group of drugs. Intravenous physostigmine temporarily improves memory tests.<sup>75</sup> Oral physostigmine has also been responsible for short-term<sup>74,76,77</sup> and long-term<sup>78a</sup> benefits in cognitive function. There appears to be a therapeutic window with physostigmine in that higher doses may have a detrimental effect.<sup>72</sup> It has been recommended that clinical trials with this agent utilize two phases, a dose finding phase and a therapeutic phase,<sup>72</sup> although this has recently been disputed.<sup>78b</sup>

Very promising results were generated in a recent study using oral tetrahydroaminoacridine (THA).<sup>79</sup> This potent anticholinesterase has a longer half-life than physostigmine and fewer peripheral side effects. It was initially tested in a pilot study in 1981 by Summers and others<sup>80</sup> with positive results. A subsequent trial in moderate to severe Alzheimer's patients demonstrated significant improvement on assessment scales, learning tests and activities of daily living as compared to placebo.<sup>79</sup>

An earlier negative trial was conducted by Kaye and others.<sup>81</sup> With both investigators lecithin was employed in addition to THA.<sup>79,80,81</sup> Lower doses of drug and shorter duration of intake might have accounted for the less impressive results of the study by Kaye.<sup>81</sup>

Current studies are being performed with THA because of the compelling need to validate the above outcome. A consistent improvement in initiative is present in a portion of the THA treated patients. This is lost during washout. Cognitive change is not similarly affected. (S.Gauthier, personal communication).

In spite of the attention given to the THA study reported in the New England Journal of Medicine,<sup>79</sup> there has been some reasonable concern about the validity of the measures used to test change in intellectual function.<sup>82,83,84,85</sup> Serial validated scales or specific memory tests might have been better accepted.



### Postsynaptic Agonists

Cholinergic function can be enhanced by another method, namely direct stimulation of post synaptic receptors which are not affected in Alzheimer's disease.<sup>70,72</sup> This bypasses the presynaptic neuron which is most likely the one pathologically involved in the disease process. Available direct cholinergic agonists are arecoline, RS - 86, bethanecol, oxotremorine and pilocarpine.

Arecoline afforded slight improvement in a small group of patients on one task when given intravenously.<sup>75</sup> No further interest in this compound has been generated due to its very short half-life. A small study found pilocarpine to be unhelpful.<sup>72</sup> Oxotremorine needs evaluation in therapeutic trials and holds some promise because of its longer half-life.<sup>72</sup> RS - 86 has been studied in two trials.<sup>86,87</sup> An ambitious trial was designed by Wettstein and Spiegel,<sup>86</sup> but only five subjects completed the study due to side effects and statistical analysis could not be done. The clinical impression, some of the psychometric tests and the Nurses Observation Scale for Inpatient Evaluations (NOSIE) suggested improvement on drug. A negative trial was reported by Bruno and colleagues.<sup>87</sup> Bethanecol given subcutaneously improved reaction time at 15 minutes following injection in a group of Alzheimer's patients compared with controls.<sup>88</sup> The paradigm involved depressing a switch when a red light was flashed. All patients with Alzheimer's disease had a longer reaction time compared with non-demented controls.

### Others

4-Aminopyridine is felt to produce increased release of acetylcholine through transmembrane calcium influx.<sup>14</sup> One study showed encouraging results with this compound with respect to memory function in Alzheimer's patients.<sup>89</sup>

Intracranial infusion therapy with a cholinergic agonist (bethanecol) has been studied. Premature positive results were based on family reporting.<sup>90</sup> Memory tests were later stated to be unchanged.<sup>91</sup> Forty-five patients have been examined recently in a double blind trial. Test scores were improved but this was not reflected in a clinical change. (S.Gauthier, personal communication).

Gerovital-H3 is a procaine formulation with some monoamine oxidase inhibitor activity.<sup>71</sup> It can be purchased in the United States although it is not approved by the Federal Food and Drug Administration for the treatment of dementia.<sup>71</sup> The majority of the controlled clinical trials with this substance have found it to be ineffective.<sup>11</sup>

Hyperbaric oxygen has not been found to improve cognitive function when tested in a controlled manner.<sup>11</sup>

### Considerations Concerning Clinical Drug Trials in Dementia

The first and foremost issue in designing a clinical trial in dementia is to aim for a homogeneous population. There is a margin of clinical error in diagnosing Alzheimer's disease, but hopefully the new guidelines set forth by the NINCDS will reduce this.<sup>92</sup> It is important not to include multi-infarct dementia in a clinical drug trial for Alzheimer's disease and therefore a modified Hachinski scale is often employed.<sup>93</sup>

With respect to enrollment, a difficult issue is informed consent. If the subject is only mildly impaired he/she can compre-

hend the implications of the study. Otherwise consent by proxy may be required. A recent study showed that consent in this manner is frequently denied.<sup>94</sup>

The control group may be studied in a parallel fashion or each subject may be his own control in a cross-over design. Although crossover design is popular with the subjects because each can be guaranteed a treatment phase, it raises some difficulties. It should only be used in conditions where the baseline is stable over time. This is not the case with Alzheimer's disease. In addition, a carry over effect may be encountered from drug to placebo phase.<sup>95</sup>

Drug dosing may be required. As with physostigmine a therapeutic window may exist and dose titration is often very helpful.<sup>72</sup> In assessing outcome one aims to sample a variety of cognitive functions which are characteristic of the deficits seen in Alzheimer's disease. The psychological tests should have alternate forms for repeated administration.<sup>16</sup> Tests which are well known and validated are best in order to compare data with other studies. Weschler memory scale,<sup>96</sup> selective reminding test,<sup>97</sup> Buschke memory scale<sup>97</sup> and Boston naming test<sup>98</sup> fulfill these criteria. Visuospatial function can be tested with block counting<sup>99</sup> or the road map test.<sup>100</sup> Mental status scales are useful for inclusion criteria but should not be depended upon for measurement of outcome, because of their lack of specificity.

A quality of life assessment should be included, such as the nurses observation scale of inpatient evaluations (NOSIE)<sup>101</sup> or the instrumental activity of daily living scale (IADL-E).<sup>102</sup> There were remarkable changes in the activities of daily living in the recent THA trial that were of considerable functional importance, but a quality of life scale was not employed.<sup>79</sup>

In a population in which memory is impaired, it is not surprising that compliance with medication is sometimes a problem. Family members should be involved with the ambulatory population. A shorter study design and a simple dosing schedule will help minimize compliance difficulties. Compliance is monitored through capsule count or plasma drug measurements. There is no method of preventing the subject from ingesting all the remaining supply just before the clinic visit. Clinical drug trials with this particular population pose a challenge to the investigator.

### CONCLUSIONS

A pharmacological approach to the clinical trials in dementia has been presented. Rationale for the use of each group of drugs and the current results of testing were discussed. It is clear that certain categories of drugs such as the cerebral vasodilators and the psychostimulants are no longer popular. Interest is active in the field of neurotransmitters, particularly cholinergic therapies. However, many other drug therapies are competing for the attention of investigators currently preoccupied with cholinergic agents.

Studies have been published producing great sensationalism,<sup>79,90</sup> only later to be criticized for flaws in design.<sup>82-85</sup> This results from the lack of standard cognitive tests and a truly successful prototypic trial with which to compare. For the time being, responsibility rests on the clinical investigator to carefully choose the intended population and to employ validated assessment instruments.

A decision should be made a priori as to what a clinically relevant change is. The percentage change expected will depend

on the individual task. One group of investigators is using videotape for following change (D. R. McLachlan personal communication). This is a costly technique but outcome will be available for anyone to view.

A major deficiency in all the studies above is the lack of pharmacokinetic data. Pharmaceutical companies test these drugs on young healthy volunteers. There are well recognized pharmacokinetic changes in the elderly<sup>103</sup> which are not taken into account in these studies. Most of the trials do not include serum levels of the drug employed. The bioavailability of these agents in the elderly is mostly unknown.

Although there will continue to be a strong social and clinical interest in drugs of this nature, progress can only be made in the field with a better understanding of the pathophysiology of Alzheimer's disease. Only then can we hope to develop drugs which might slow down the progression of this devastating disorder.

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