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## Cognition Enhancers

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## Executive Summary

The search for treatments for dementia, alongside other scientific and societal changes, has prompted the development of symptomatic treatments and disease-modifying drugs for people with degenerative brain diseases, mild cognitive impairment, and psychiatric diseases that involve cognition impairment. The enhancement of aspects of cognition, such as learning and memory, now seems possible for people with normal age-related decline and in healthy people, although so far the effects of these cognition enhancers are modest. The next two decades are likely to bring deeper knowledge of the mechanisms of learning, memory, and forgetting, together with an understanding of the relationship between changes in molecules, cells and brain circuits, and changes in cognition. Already, research efforts by the pharmaceutical industry are poised to deliver many more disease modifiers and putative cognition enhancers, though limitations exist in translating laboratory findings into effective interventions for human use.

If effective interventions become available, their general use will bring health, social, ethical and regulatory issues. The widespread use of cognition enhancers for healthy people could have substantial impact and potentially become problematic – a minority may have abuse liability. Mechanisms do not exist currently to regulate cognition enhancers for non-medical purposes, though social changes together with commercial pressures mean that their use for enhancement is likely to be increasingly required, desired and accepted. Their use for disease-related impairments seems unlikely to cause concerns if cost-effective treatments are used to enhance function and quality of life. New challenges will include the development of biomarkers to allow early intervention and the targeting of therapies for the best effect on the individual.

## Definitions and scope of review

'Cognition enhancement' is the use of various strategies to boost cognitive functions – i.e. mental states that underpin information-processing tasks such as attention, memory, and selective forgetting. The term was originally used for the treatment of disease-associated cognitive impairment, such as in dementia and schizophrenia. Subsequently, the term expanded to encompass the use of interventions for mild cognitive impairment (MCI), currently defined as cognitive deficits that do not overtly impair function. MCI has a greater risk of progression to dementia than for age-related cognitive decline, which is probably synonymous with normal ageing (Figure 1). Now 'cognition enhancement' is applied to the use of interventions for normal ageing and in well people for non-medical purposes. Many agents are marketed to UK consumers as cognition enhancers or nootropics. This term describes substances thought to enhance mental functions, and is interchangeable with 'smart drugs' or 'smart pills'. Definitions of pharmacological terms are given elsewhere.<sup>1</sup>

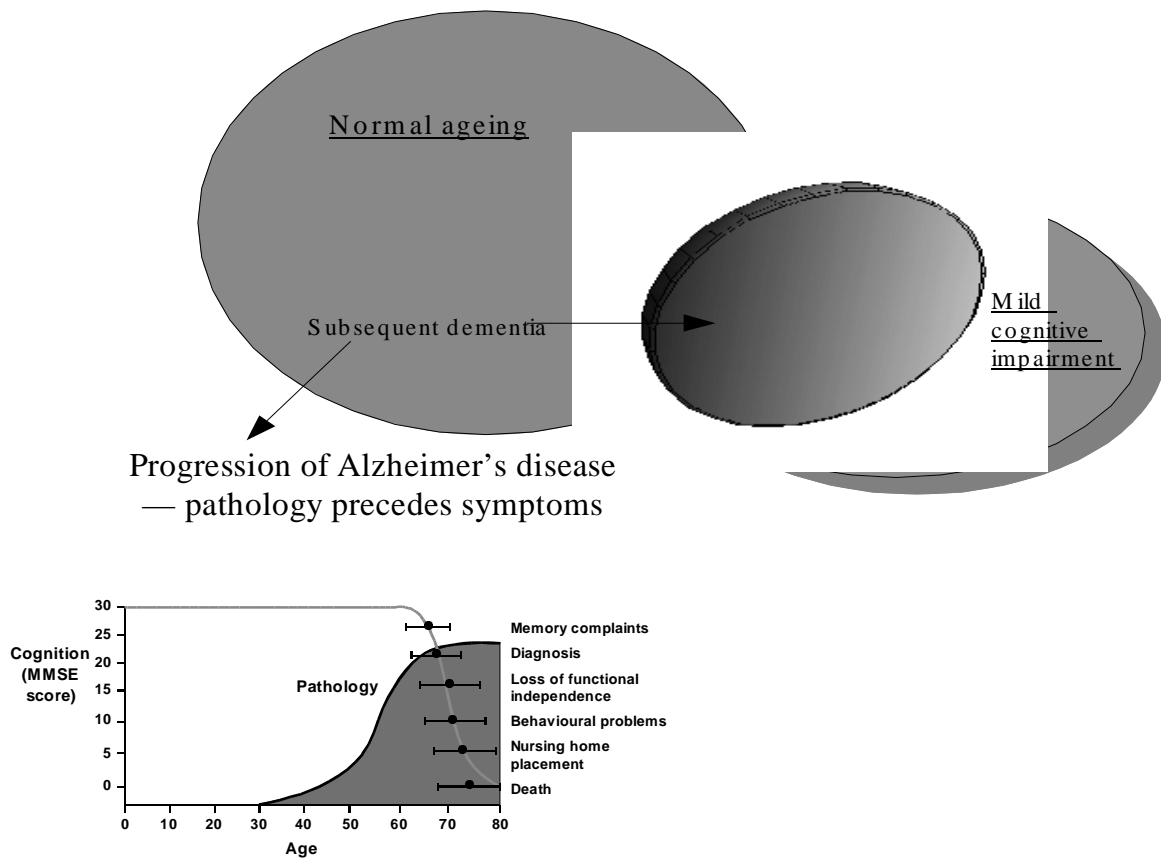


Figure 1: **Progression to dementia in normal ageing versus mild cognitive impairment** – the latter might be linked with early pathology.

This review is not a comprehensive account of dementia treatment or of all agents with cognition-enhancing properties. The pace of change is such that new developments are likely to be announced almost as soon as this review is published. Instead, we offer a representative account of the underlying science, current and potential agents, and strategies for drug development, plus forward-looking predictions of the field. A particular target of cognition enhancers is augmentation of learning and memory, and these are the focus of this review. However, our review and predictions apply to other functions, such as attention and selective or useful forgetting, as well as to traditionally non-cognitive aspects of subjective experience such as mood and empathy.

## Background

Advances in our understanding of central nervous system functioning in health and disease have brought with them the potential for altering that functioning with psychoactive substances. The search for interventions that might halt cognitive decline was initiated within dementia research, and then applied to Parkinson's Disease (PD) and other neurodegenerative and neurodevelopmental conditions such as schizophrenia and epilepsy.

Alongside the development of such disease-modifying drugs, changes in society and attitudes have occurred. People in the UK and similar nations are living longer. The current generation aged over 55 is also the richest in history, and aspires to an active retirement free from illness. However, age-related memory impairment begins to accelerate from 55 years, and the likelihood of having Alzheimer's Disease (AD) or a related dementia substantially rises in old age, with 20% of those aged over 80 affected. Now the most common reason for nursing home admission is not physical

but cognitive impairment.

Within the past few decades, the pre-programmed decline in body systems that occurs with ageing has become a target for intervention, in addition to the prevention of age-related diseases such as AD. Increasing public interest in technologies for enhancement beyond therapy or prevention has encompassed the possibility of cognitive improvement in healthy people. Notably, the Cochrane Dementia and Cognitive Impairment Group, registered in August, 1995, altered its name and scope in 2000 to the Cochrane Dementia and Cognitive *Improvement* Group (CDCIG).

By 2010, the market for AD therapy alone is expected to grow from 16 million patients to 21 million in the seven major pharmaceutical markets, while AD drug sales could exceed \$8 billion.<sup>2</sup> (£4.4 billion) Substantial numbers of people already exist with other neurodegenerative conditions (e.g. PD), with MCI, or with cognitive decline due to psychiatric disease. This group may be additionally important because depressed elderly people, like those with MCI, may have an increased risk of progression to dementia.<sup>3</sup> Added to these trends is the over-the-counter and Internet availability of cognition-enhancing agents, while consumers are more informed about psychoactive substances, and more likely to take a preventative approach to future cognitive decline. Already, early intervention in neurodegenerative and related diseases is a public priority.

Research on cognition, neuroscience, and ageing has provided a multidisciplinary platform to inform development of disease-modifying drugs and, more recently, potential cognition enhancers. Key developments include: animal models, including transgenic animals with added or deleted genes to help indicate potential cognitive mechanisms,<sup>4</sup> imaging techniques to investigate brain structure and functional activity,<sup>5</sup> and increasingly sophisticated neuropsychological testing of cognitive functions.<sup>6</sup> Although the correspondence between these various strands of evidence remains unclear, for example, how neuropsychological deficits relate to changes in brain structure and functioning – the emerging field of cognitive neuroscience has begun to relate them and apply the findings to normal ageing and disease states.<sup>7,8</sup>

### **Basis of learning and memory**

Much has been discovered about the cellular and molecular basis of learning and memory in several species, although we still do not know comprehensively how new information is perceived, stored, consolidated, and retrieved or forgotten over timescales that vary from seconds to decades. The next 20 years are likely to bring much greater understanding of learning and memory, and our ability to manipulate these pathways will undoubtedly increase.

The central mechanism thought to underpin memory is synaptic plasticity<sup>9</sup> – changes in the strength and size of synapses that increase or decrease efficiency of transmission. Roles in learning, memory and forgetting are also attributed to new synapse formation (synaptogenesis) and loss, the proliferation and survival of new neurons (neurogenesis), and neuronal cell death (neurotoxicity and apoptosis). Each process provides possible targets for cognition enhancement and selective forgetting in healthy people, while processes important in disease-associated cognitive decline are important targets for early therapeutic intervention. Figure 2 shows the dramatic brain atrophy seen in AD compared with a healthy person.

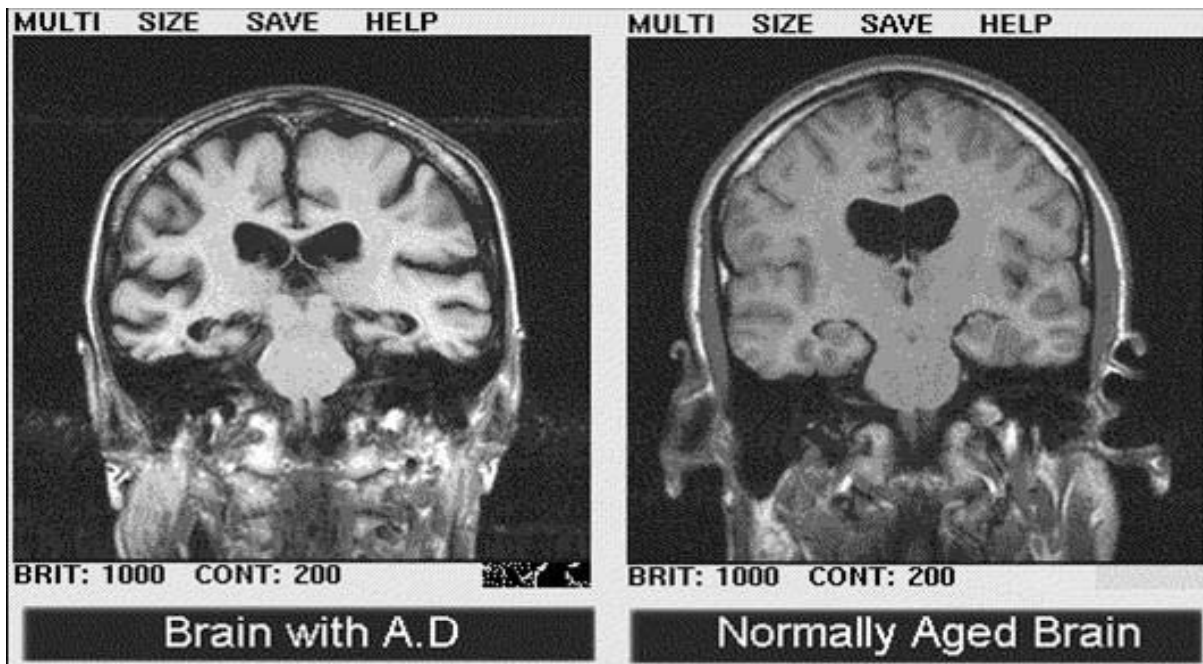


Figure 2: Gross differences in brain structure between Alzheimer's Disease and normal ageing

### Long-term potentiation

The fundamental model of synaptic plasticity is long-term potentiation (LTP) – an increase in synaptic signalling after the synchronised stimulation of connected neurons. One classic example of LTP involves binding of the neurotransmitter glutamate to NMDA (N-methyl-D-aspartate) receptors. Glutamate binding opens a channel in the receptor, allowing charged atoms (ions) to flow into the cell. At rest, the NMDA receptor channel is plugged by magnesium ions, so glutamate binding opens the channel but ions cannot flow through. When the membrane gains positive charge due to the transmission of an electrical signal, the magnesium ions leave the channel. When NMDA receptors open, calcium ions flow in to trigger a cascade of molecular events,<sup>10</sup> in addition to the flow of sodium ions that can result in onward transmission of the electrical signal.

Potentiation arises because short-term calcium-triggered events increase the sensitivity of the cell to further signals, so when a particular event is repeated, persistent and increasing activation of that circuit results in learning. The calcium influx acts to increase the sensitivity and number of a second glutamate receptor – AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid),<sup>10</sup> which increases the amount of sodium ions allowed into the cell with each stimulation, further increasing the strength of synaptic signalling.

More permanent changes that could underlie longer-term memory require the synthesis of new proteins,<sup>11</sup> in both presynaptic and postsynaptic neurons.<sup>10</sup> In humans, CREB (cyclic-AMP response element binding protein) is one factor that facilitates protein production.<sup>12</sup> Inward calcium flow indirectly activates CREB, which induces gene expression. Increased gene expression can lead to production of more receptors, as well as structural proteins that 'cement' the synaptic connection between two repeatedly communicating neurons. Presynaptic strengthening may also involve the addition of new receptors, and thus synapse size is increased on each side. Another important process is the production of neurotrophic factors that stimulate nerve growth and increase the complexity of neural connections, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Roles in other short-term and longer-term more complex changes in brain and behaviour are beginning to be assigned to neurotrophic factors.<sup>13</sup>

The formation and storage of very long-term memories is not well understood but some authors propose self-perpetuating reactions, such as those involving protein kinases and CREB, as one ongoing mechanism.<sup>14</sup> The state of activation or depression in individual neural circuits may need reinstatement by repeated activation or depression, while synaptic weakening may be important to remove unnecessary connections. These two processes may particularly occur during sleep.<sup>15,16</sup>

Synaptic plasticity occurs in several brain structures. For example, the hippocampus has been implicated in encoding memories, in short-term or working memory, and in contextual learning or sequential memory (such as travel routes), while the neocortex is implicated in long-term memory storage and recall.<sup>10,17</sup> The cerebellum has been implicated in learning direct and especially timed actions, such as riding a bicycle,<sup>18</sup> while the amygdala seems key to emotion-related memory.<sup>19</sup>

#### Effects of attention, emotion and stress

Several factors affect the success of LTP and its inverse state, long-term depression (LTD). Neurotransmitters like acetylcholine, dopamine, serotonin, and CRF (corticotrophin-releasing factor) can alter the strength of LTP and LTD. The counterpart in the whole organism is likely to be effects of attention, stress and emotion on cognition.

Acetylcholine may play a key part in focusing learning and memory, and the loss of cholinergic projections is a classic feature of dementia. Activation of these projections can enhance LTP, at least in the hippocampus.<sup>20,21</sup> Serotonin has been shown to both promote and inhibit learning,<sup>22,23</sup> while dopamine acts to potentiate both LTP and LTD, depending on interactions between receptors.<sup>24</sup> Other neurotransmitters implicated in enhancing LTP include neuropeptides, such as somatostatin.<sup>25</sup>

The effects of stress on memory are complex, and depend on the type and phase of memory, the stressor involved, and its timing and duration. Glucocorticoids (steroid stress hormones) interact with noradrenaline, dopamine, and perhaps acetylcholine to generate appropriate learning responses for acutely stressful situations. High glucocorticoid levels impair memory retrieval but improve memory consolidation in fearful situations, but not in simply novel, arousing situations.<sup>25,26</sup> Thus, fearful situations may produce strong new memories that 'overwrite' old memories, leading to amnesia for previous related knowledge.<sup>27</sup> In such situations, the amygdala may generate new emotion-related memory while simultaneously the hippocampal-prefrontal cortex circuit is impaired.<sup>28</sup>

In the long term, high glucocorticoids impair several learning-related processes.<sup>29</sup> Other inhibitory states, including those with high levels of GABA (gamma-aminobutyric acid),<sup>30</sup> cannabinoids,<sup>31</sup> and inflammatory immune chemicals<sup>32</sup> may impair both new memory and the retrieval of old learning. Endogenous cannabinoid signalling appears to be important in extinguishing aversive memories.<sup>33</sup>

#### Ageing, MCI and disease

Any process that leads to cognitive impairment, including normal ageing, may impact on common structures and processes, including LTP and LTD, neural connectivity, cellular calcium regulation, protein formation and destruction (proteolysis), neurotransmitter and hormone levels, and cerebral blood flow.<sup>34-39</sup> Neural connectivity involves the formation, survival, and loss of synapses and neurons and effects on dendrites (nerve filaments) and dendritic spines where synapses form. Many of these processes are inter-related. Calcium regulation also seems important for dendritic changes, while abnormal protein formation can induce neurotoxicity. Finally, the balance between disruptive and compensatory mechanisms, such as the ability to recruit new brain regions to perform specific tasks is thought to be crucial in determining clinical cognitive impairment.<sup>8</sup>

Normal ageing, MCI and early disease thus share similarities, although some of the changes seen

during normal ageing seem distinct from established disease pathology. For example, normal ageing shares some similarities with AD, such as the presence of  $\beta$ -amyloid plaques, reduced blood flow, neuropeptide changes, and reduced cholinergic function, but not others such as neurofibrillary tangles and neuritic plaques. Whether normal ageing, MCI and AD represent a spectrum of outcomes or different entities is debated – more likely, a subset of people with MCI have early AD.<sup>8,40</sup> But while the relationships between normal ageing, MCI and various disease processes await full definition, the study of what seem to be individual entities may inform understanding of others, such as the loss of neural connectivity in ageing, AD and schizophrenia<sup>36</sup> or the disruptions in proteolysis that underlie different neurodegenerative diseases.<sup>37</sup>

Notably, disease processes start several years earlier than clinical problems. Some of those affected will be categorised with MCI, while up to 60% of people with MCI show such pathology. A far higher proportion of people with MCI will develop dementia than those with normal age-related deficits, so genetic, neurochemical and imaging tests are in development to distinguish potential signs of early disease.<sup>40, 41</sup> Development of such biomarkers could allow early intervention with disease-modifying drugs. Since some early disease changes may be shared by those with normal ageing, the distinction between disease modification and cognition enhancement might be somewhat artificial. However, this distinction allows us to consider cognition-enhancing agents separately.

### **Current cognition enhancers**

Many different strategies are proposed to enhance cognition. Most interventions target either disease pathologies or the processes underlying normal cognition, particularly synaptic plasticity. Many act via more than one pathway or target. Strategies and treatments for cognition enhancement include:

- general measures such as exercise and environmental enrichment
- correction of underlying factors such as hypertension
- nutrients
- herbal medicines
- pharmaceuticals
- psychological and learning strategies<sup>6</sup>
- electromagnetic interventions e.g. transcranial magnetic stimulation, brain-computer interfaces.<sup>42</sup>

#### General measures

Environmental enrichment alters the structure of rodent brains and improves learning and memory, apparently by changes in gene expression related to neuron structure, synaptic plasticity, and transmission.<sup>43</sup> Such changes might be prompted via neurotrophin expression (e.g. BDNF).<sup>13</sup> Parallel findings in elderly people are that leisure activities and physical exercise are linked with lower risks of dementia and cognitive decline respectively.<sup>44,45</sup>

#### Correction of underlying factors

Cognitive impairment has been linked with hypertension, high cholesterol levels, diabetes and possibly the menopause. Early correction of some of these might slow cognitive decline.

Several randomised controlled trials (RCTs) have investigated the effects of lowering blood pressure on risk of dementia, although a Cochrane review is awaited.<sup>46</sup> One large trial (Syst-Eur)

found that nitrendipine, a calcium-channel blocker, plus add-on medications was associated with a 50% reduction in dementia, compared with a placebo,<sup>47</sup> which increased with longer follow-up.<sup>48</sup> However, this finding could be related to other effects of calcium-channel blockers (see below). Further, a recent study found that use of brain-penetrating angiotensin-converting enzyme inhibitors (but not non-brain-penetrating agents nor calcium-channel blockers) slowed progression of AD.<sup>49</sup>

A Cochrane review on diabetes management and cognitive impairment reviewed five trials, but none were of sufficient quality.<sup>50</sup> A Cochrane review on statins for AD found a similar lack of available trials.<sup>51</sup> Other evidence on the effect of statins is contradictory<sup>52,53</sup> so the possibility of an additional benefit on cognitive impairment remains open.

The Cochrane review on hormone-replacement therapy (HRT) for menopausal symptoms found five small trials, none of which provided convincing evidence of delay in the progression of dementia.<sup>54</sup> A similar conclusion was drawn over nine trials on protection from cognitive impairment.<sup>55</sup> The US Women's Health Initiative Memory Study indicated more than doubling of dementia risk in women on HRT and aged 65 years or more.<sup>56</sup> These and unrelated concerns have led to cautions against the use of HRT in older women, especially those with dementia. Soya extract, which contains oestrogen-like compounds, was given to postmenopausal women in an RCT that reported some benefits on cognition after 12 weeks.<sup>57</sup> The long-term consequences of a high soya diet continue to be debated.

### Nutrients and 'nutraceuticals'

Many dietary supplements are recommended by various sources to improve cognition, including 'nutraceuticals' – dietary components or similar that act like drugs. These agents are widely available in UK retail outlets. Such agents are usually well tolerated and no abuse potential is known for those listed.

Table 1 summarises all specific dietary supplements reviewed by the CDCIG that are regulated in the UK under the Food Safety Act 1990.

**Table 1: Potential cognition enhancers available as dietary supplements in the UK**

#### **Summary of Cochrane reviews**

| Name        | Proposed mechanism  | Evidence   | Conclusion  | Comments   |
|-------------|---|--|---|--|
| Vitamin E   | Antioxidant-scavenging of free radicals                                 | Cochrane review (update 2002) in AD <sup>59</sup>                    | Insufficient evidence of efficacy   | Included only one RCT of vitamin E, selegiline or both                         |
| Vitamin B6  | Treatment of undetected deficiency and reduction in homocysteine levels | Cochrane review (update 2003) for cognition <sup>60</sup>            | No evidence for short-term benefit in healthy people but more RCTs needed | Included two trials in healthy people only. Both papers report memory benefits |
| Vitamin B12 | As for B6   | Cochrane review (update 2003) for cognitive impairment <sup>61</sup> | Insufficient evidence of efficacy   | Included two trials of people with dementia and low B12                        |

| <b>Table 1: Potential cognition enhancers available as dietary supplements in the UK</b> |   |   |  |  |
|--|---|---|--|--|
| <b>Summary of Cochrane reviews</b>   |   |   |  |  |
| Folate   | As for B6   | Cochrane review (update 2003) for people with cognitive impairment or healthy elderly <sup>62</sup>                         | No significant benefit of folate supplementation with or without B12 – important issue that needs further RCTs | Four RCTs were included, one in healthy elderly people. One studied combined B12/folate supplements            |
| Thiamine   | Previous evidence for benefit of thiamine in AD   | Cochrane review (update 2003) for AD <sup>63</sup>  | Not possible to draw any conclusions   | Included three studies that amounted to less than 50 participants overall                                      |
| Thiamine   | Alcohol misuse results in thiamine deficiency, which can lead to cognitive impairment as part of Wernicke-Korsakoff syndrome                              | Cochrane review (update 2003) for people with or at risk of Wernicke-Korsakoff syndrome due to alcohol misuse <sup>64</sup> | Insufficient evidence to guide prescribing for prophylaxis or treatment  | Included one trial only, which reported benefit with high dose intramuscular thiamine (200mg/day) after 2 days |
| Lecithin(phosphatidyl-choline)   | A cell membrane component and the major dietary source of choline needed to synthesise acetylcholine  | Cochrane review (update 2003) for cognitive impairment including dementia <sup>65</sup>                                     | Available evidence does not support use for dementia, although a moderate effect cannot be excluded            | Included 12 RCTs – only one trial, of subjective memory problems, reported dramatic effects                    |
| DHEA and DHEA sulfate  | Neurosteroids that enhance glutamate effects and inhibit GABA effects. Antiglucocorticoid action may lead to neuroprotective and immune-enhancing effects | Cochrane review (update 2004) for cognitive function <sup>66</sup>  | No support for an improvement of memory or other cognitive functions   | Three studies of healthy older people, and one in perimenopausal women with decreased well-being               |
| Alpha-lipoic acid  | Several mechanisms, including enhanced mitochondrial function and antioxidant properties  | Cochrane review (update 2004) for dementia <sup>67</sup>  | No RCTs included, thus use cannot be recommended   | Benefit proposed from non-randomised trials and pre-clinical research only                                     |
| Acetyl-L-carnitine   | Similar roles to alpha lipoic acid  | Cochrane review (update 2003) for dementia <sup>68</sup>  | Evidence for benefit on clinical global impression only, thus no evidence to recommend routine use             | 11 RCTs included, all in people with AD  |

**Table 1: Potential cognition enhancers available as dietary supplements in the UK****Summary of Cochrane reviews**

|               |   |   |   |  |
|---------------|---|---|---|--|
| Ginkgo biloba | Multiple actions, including vaso-dilatation, anticoagulation, antioxidant actions, and effects on neurotransmitters | Cochrane review (update 2002) for cognitive impairment and dementia <sup>69</sup> | Highly variable trial quality and inconsistent results even among better trials | Large, high-quality long-term trial needed, given inconsistent effects and good safety |
|---------------|---|---|---|--|

*Vitamin E +/- other antioxidant vitamins*

Free radicals such as toxic oxygen products are linked with neuronal damage in AD and might be important in normal ageing. A recent review of dietary factors in AD<sup>58</sup> included seven cohort studies that related vitamin E intake (including supplements) to the risk of cognitive impairment, including dementia. All studies considered dietary sources with and without vitamin C supplements, and three also investigated carotenoid intake. One study found no relation between antioxidant intake and AD, while three found an inverse relationship between dietary intake of vitamin E and dementia. The other three studies explored use of supplements. All found some benefit of vitamin E and C supplementation, one reported a reduced risk of vascular dementia (but not AD), one a reduced risk of AD, and one increased global cognition scores.

The 2002 Cochrane review included only one randomised trial of vitamin E, selegiline, both or placebo in AD.<sup>59</sup> Although vitamin E was linked with a greater effect than selegiline or combined treatment, falls were increased in the vitamin E arm. For cognitive impairment in healthy elderly people, one good-sized trial found little effect of antioxidant vitamins for up to 12 months.<sup>70</sup>

*Vitamins B6, B12, and folate*

Deficiencies of vitamins B6, B12, and folate reduce the conversion of homocysteine to methionine or cysteine, while raised homocysteine has been linked with cerebrovascular disease and neuronal toxicity. Some evidence exists from epidemiological and non-randomised studies that reduced homocysteine levels or increased B6, B12, and/or folate can reduce dementia risk or improve cognition, although not all studies found positive findings.<sup>58</sup>

Deficiency of vitamin B6 is linked to various neuropsychiatric disorders and the rationale for its use is to treat undetected deficiency. A Cochrane review found no significant differences with treatment,<sup>60</sup> although individual papers have reported significant improvements in aspects of memory performance.

B12 deficiency affects more than 10 per cent of older people, and is associated with neuropsychiatric disorders. Folate deficiency has been linked to cerebral cortical atrophy at autopsy. One Cochrane review included two small randomised trials in demented people with low B12, and found no significant benefit on cognitive impairment.<sup>61</sup> A second Cochrane review included four RCTs of folic acid with or without B12 for healthy people, or individuals with cognitive impairment or dementia.<sup>62</sup> All trials found no significant benefits.

*Thiamine and alcohol*

Thiamine has been the treatment of choice for Wernicke-Korsakoff syndrome for 50 years. This syndrome, caused by thiamine deficiency, is most commonly due to heavy alcohol intake. Thiamine

replacement can reverse early cognitive changes and is commonly prescribed,<sup>71</sup> although evidence to guide prescribing is virtually non-existent.<sup>64</sup> High and no alcohol intake in middle age is linked with later cognitive impairment<sup>72</sup> while moderate alcohol intake may be protective against dementia,<sup>58</sup> except in those with the APOE epsilon-4 allele.<sup>72</sup> Whether a link exists between cognitive impairment and thiamine deficiency cannot be determined from current evidence.<sup>63</sup>

#### *Choline precursors and membrane components*

Various choline precursors such as the major dietary phospholipid lecithin (phosphatidylcholine) – have been used in an attempt to accelerate acetylcholine synthesis. Lecithin is also a key component of neuronal cell membranes, which are degraded during cerebral ischaemia to free fatty acids and free radicals. A Cochrane review<sup>65</sup> of 12 trials of lecithin, involving 265 people with AD, 21 people with PD, and 90 people with subjective memory problems, did not find any substantial effects, except in the study on memory problems. The authors conclude that a moderate effect cannot be excluded but a large RCT is not a priority. Some beneficial effects have been reported for the related phosphatidylserine,<sup>73</sup> although overall the evidence is inconclusive.

Marine-derived omega-3 fatty acids, especially docosahexaenoic acid, are purported to improve cell-membrane fluidity and cause less damage on membrane degradation than omega-6 fatty acids. Five cohort studies have explored the link between fats, fish intake, and risk of dementia or AD.<sup>58</sup> Overall, these studies suggest that high fish intake, unsaturated fats, and omega-3 fatty acids may be protective. Few trials have been done on marine-derived fatty acids for cognitive impairment, except for those trials done in preterm infants. One RCT reported abnormal levels of essential fatty acids in 36 patients with AD, and found a significant benefit of supplementation.<sup>74</sup>

#### *Neurosteroids and melatonin*

Dehydroepiandrosterone (DHEA) and its sulphate DHEAS are neurosteroids that enhance glutamate signalling and reduce GABA inhibition. Their antigluccorticoid action may have neuroprotective and immune-enhancing effects. Some, but not all, studies have found lower levels of DHEA/S in people with dementia. However, a Cochrane review of four trials in people without cognitive impairment found few significant findings.<sup>66</sup> The authors suggest that benefit may be evident only in large, longer trials.

Melatonin is a hormone with clock-setting properties that is secreted at night from the pineal gland, at levels that decrease with ageing. Positive effects of melatonin have been reported on sleep and cognition in elderly people<sup>75</sup> and in people with dementia,<sup>76</sup> although other trials have been negative. A Cochrane review is planned.<sup>77</sup>

#### *Other endogenous antioxidants*

Two endogenous antioxidants – alpha-lipoic acid and acetyl-L-carnitine – have been studied in people with dementia. Both are important in energy metabolism and might protect against oxidative damage to brain genetic material, thus improving memory.<sup>78</sup> However, a Cochrane review found no suitable RCTs of alpha-lipoic acid, and benefit in two small non-randomised studies.<sup>67</sup> A reasonable body of evidence exists for global benefits with short- to medium-term use of acetyl-L-carnitine in AD, but without apparent benefit in most other measures.<sup>68</sup> Thus global benefits may be due to chance.

#### Herbal medicines

Use of herbs for cognitive improvement occurs in many traditions, including Chinese, Ayurvedic, and European herbalism. Usually herbal preparations are well tolerated but they can have harmful side-effects, including interactions with pharmaceuticals.<sup>79,80</sup> The only herb that has been reviewed by the CDCIG is *Ginkgo biloba*,<sup>69</sup> commonly used for memory disorders and often also taken with ginseng (e.g. *Panax ginseng*).<sup>81-83</sup> Some herbs with evidence of cognition-enhancing action are

listed in Table 2.<sup>81-85</sup>

The European Commission adopted a Directive on Traditional Herbal Medicinal Products (30 April 2004), prompted by concerns over public protection from the sale of ineffective or potentially harmful products. The UK has until October 2005 to implement the Directive, although herbs legally available on 30 April 2004 receive transitional protection until April 2011.

### *Ginkgo biloba and ginseng*

Extracts of *Ginkgo biloba* leaves are prescribed in Germany and France for cerebral insufficiency, memory and concentration problems. A recent Cochrane review found that the quality of trials is highly variable. Moreover, trials with superior methodology have inconsistent results.<sup>69</sup>

Nevertheless, most studies report at least some improvement in the overall functioning, cognition and activities of daily living in people with dementia. The authors advise that a large, high-quality trial is needed. A large trial is now underway (2005) in London. A potentially hazardous interaction could occur with anticoagulant drugs such as warfarin and aspirin.<sup>79</sup>

Many studies have been done in healthy people to assess whether ginkgo has positive effects. A review of nine trials found mixed results, which could be explained by dose variations.<sup>86,87</sup> A Cochrane review of the effect of ginkgo on cognition in healthy populations is planned.<sup>88</sup>

Ginkgo is thought to act in several ways<sup>69,89</sup> including vasodilatation, anticoagulant effects, antioxidant actions, neuroprotection, and neurotransmitter changes. Ginkgo is often taken together with ginseng (e.g. *Panax ginseng*) as the two are traditionally said to be synergistic.<sup>81,82</sup> *Panax ginseng* is reported to have multiple effects, including neuroprotection.<sup>81,82</sup> The few studies differ on whether ginseng has cognition-enhancing properties in healthy people.<sup>90-92</sup> Ginseng is reported to have a greater effect on brain electrical activity than ginkgo.<sup>83</sup>

**Table 2: Some putative cognition-enhancing herbs<sup>81-85</sup>**

|                                |                               |                               |
|--------------------------------|-------------------------------|-------------------------------|
| <i>Acorus calamas</i>          | <i>Embelia ribes</i>          | <i>Nicotiana tabacum</i>      |
| <i>Angelica archangelica</i>   | <i>Emblica officinalis</i>    | <i>Paeonia emodi</i>          |
| <i>Asparagus racemosus</i>     | <i>Eugenia caryophyllus</i>   | <i>Panax ginseng</i>          |
| <i>Bacopa monniera</i>         | <i>Evodia rutaecarpa</i>      | <i>Piper longum</i>           |
| <i>Biota orientalis</i>        | <i>Galanthus nivalis</i>      | <i>Polygala tenuifolia</i>    |
| <i>Boerhavia diffusa</i>       | <i>Ginkgo biloba</i>          | <i>Polygonum multiflorum</i>  |
| <i>Celastrus paniculatus</i>   | <i>Glycyrrhiza glabra</i>     | <i>Pongamia pinnata</i>       |
| <i>Centella asiatica</i>       | <i>Huperzia serrata</i>       | <i>Rosmarinus officinalis</i> |
| <i>Clitoria ternatea</i>       | <i>Hydrocotyl asiatica</i>    | <i>Salvia lavandulifolia</i>  |
| <i>Codonopsis pilosula</i>     | <i>Lawsonia inermis</i>       | <i>Salvia miltiorrhiza</i>    |
| <i>Convolvulus pluricaulis</i> | <i>Lycoris radiata</i>        | <i>Schizandra chinensis</i>   |
| <i>Coptis chinensis</i>        | <i>Magnolia officinalis</i>   | <i>Terminalia chebula</i>     |
| <i>Crocus sativus</i>          | <i>Melissa officinalis</i>    | <i>Tinospora cordifolia</i>   |
| <i>Curcuma longa</i>           | <i>Nardostachys jatamansi</i> | <i>Withania somnifera</i>     |

Pharmaceuticals

Several processes are targets for current agents aimed to improve cognition, although effect sizes are modest. Table 3 summarises the evidence from the CDCIG for licensed medicines. Most of these are prescription-only medicines in the UK or elsewhere.<sup>93</sup> Few have abuse potential.

| <b>Summary of Cochrane reviews</b> |  |  |   |   |
|------------------------------------|--|--|---|---|
| Name                               | Proposed mechanism   | Evidence   | Conclusion  | Comments  |
| Donepezil                          | Acetyl-cholinesterase inhibitor                                    | Cochrane review (update 2003) in AD <sup>94</sup>                            | Efficacy in all stages of disease, for up to a year's treatment                     | Cost-effectiveness data awaited for AD treatment                    |
|                                    |  | Cochrane review (update 2003) in vascular cognitive impairment <sup>95</sup> | Benefits for probable and possible mild-to-moderate disease for 6 months            | Extension of studies and better diagnostic criteria are desirable   |
| Galantamine                        | Acetyl-cholinesterase inhibitor; also possible cholinergic agonist | Cochrane review (update 2004) in AD <sup>96</sup>                            | Consistent positive benefits in mild-to-moderate disease with 3–6 months' treatment | Daily dose of 16mg titrated over 4 weeks offered best tolerability  |
| Rivastigmine                       | Acetyl-cholinesterase and butyryl-cholinesterase inhibitor         | Cochrane review (update 2000) in AD <sup>97</sup>                            | Benefits on various markers in mild-to-moderate AD after 26 weeks of 6–12mg         | Further study needed on optimum dosage to minimise side-effects     |
|                                    |  | Cochrane review (update 2003) in Lewy body dementia <sup>98</sup>            | Benefits in some markers only if observed cases analysed                            | Evidence for efficacy is weak                                       |
| Nicotine                           | Acetylcholine agonist and releaser                                 | Cochrane review (update 2002) in AD <sup>99</sup>                            | Unable to find evidence for or against benefit                                      | One trial found, but did not present results suitable for inclusion |
| D-cycloserine                      | Partial NMDA agonist – enhances glutamate signalling               | Cochrane review (update 2002) in AD <sup>100</sup>                           | No place for this agent in treatment of AD  | Lack of positive effects in well-powered controlled trials          |

**Table 3: UK pharmaceutical drugs that act on cognition****Summary of Cochrane reviews**

|                 |  |   |  |  |
|-----------------|--|---|--|--|
| Memantine       | Moderate NMDA antagonist – may protect from excitatory cell death                  | Cochrane review (update 2004) in dementia <sup>101</sup>  | Clinically noticeable reduction in deterioration at 28 weeks   | Benefit discernible in moderate-to-severe disease only, but early benefits seen, and well tolerated            |
| Nimodipine      | Calcium-channel blocker – might reduce neuronal death due to excess calcium influx | Cochrane review (update 2002) in various dementias <sup>102</sup>                                   | Some short-term benefits in dementia due to unclassified or mixed disease, Alzheimer's, or vascular dementia | Further evaluation of unavailable trial data is desirable, and new research must focus on longer-term outcomes |
| Propentofylline | Adenosine uptake and phosphodiesterase inhibitor – also anti-inflammatory effects  | Cochrane review (update 2002) in dementia <sup>103</sup>  | Limited evidence of benefits in AD, vascular dementia, or mixed disease                                      | Review limited by unavailable data on 1,200 patients not released  |
| Selegiline      | Monoamine oxidase-B inhibitor – promotes dopamine signalling                       | Cochrane review (update 2002) in AD <sup>104</sup>  | No evidence of clinically meaningful benefit   | Further trials in AD are not justified   |
| Piracetam       | Metabolic enhancement, antithrombotic, and neuroprotectant                         | Cochrane review (update 2001) in dementia or cognitive impairment <sup>105</sup>                    | Does not support use   | Further evaluation warranted both on available data and as new studies   |
| Hydergine       | Increased cerebral blood flow, effects on neurotransmitters                        | Cochrane review (update 2000) in dementia <sup>106</sup>  | Significant treatment effects on generic scales  | Selection criteria for trials is outdated so benefit remains uncertain   |
| Nicergoline     | As above, plus antioxidant and neuroprotectant properties                          | Cochrane review (update 2002) in dementia and other age-related cognitive impairment <sup>107</sup> | Some positive benefits on cognition and behaviour in older patients with mild-to-moderate impairment         | Studies have differing outcomes; also, newer diagnostic criteria not used so not clear who might benefit       |

**Table 3: UK pharmaceutical drugs that act on cognition****Summary of Cochrane reviews**

|             |  |  |  |  |
|-------------|--|--|--|--|
| Vinpocetine | Metabolic and blood-flow enhancement, antithrombotic, neuroprotectant, phosphodiesterase inhibitor | Cochrane review (update 2002) in cognitive impairment and dementia <sup>108</sup>          | Evidence does not support clinical use   | Large trials in well-defined populations are needed to evaluate efficacy |
| CDP-choline | Precursor of phosphatidylcholine   | Cochrane review (update 2003) for chronic cerebral disorders in the elderly <sup>109</sup> | Some evidence of positive benefits on memory and behavioural disturbances (up to 3 months) | Longer trials warranted with current diagnostic criteria                 |

Acetylcholine*Cholinesterase inhibitors*

Three agents that inhibit the breakdown of acetylcholine by blocking acetylcholinesterase are licensed for treatment of mild-to-moderate AD<sup>93</sup> – donepezil, galantamine and rivastigmine. Galantamine, found in *Galanthus nivalis* and other plants, may also act via nicotinic receptors while rivastigmine also inhibits butyrylcholinesterase, which may be important in later-stage AD. The CDCIG has found beneficial effects on cognition, functioning, and behaviour for:

- donepezil in AD treated for up to a year<sup>94</sup> and vascular dementia treated for up to 6 months<sup>95</sup>
- galantamine for AD treated for up to 6 months<sup>96</sup>
- rivastigmine for AD treated for 6 months;<sup>97</sup> one trial of rivastigmine found some efficacy for dementia with Lewy bodies.<sup>98</sup>

Efficacy trials comparing the three agents have been criticised over methodology and reporting.<sup>110</sup> Cognition-enhancing effects have been reported in healthy people. Although one study of donepezil found a slight worsening on some measures,<sup>111</sup> another found some improvement.<sup>112</sup> Tolerability is generally similar for the three drugs.

*Nicotine<sup>1</sup>*

Nicotine stimulates nicotinic cholinergic receptors and also releases acetylcholine, while the metabolite cotinine might be neuroprotective. Little RCT evidence of the effects of nicotine exists in AD,<sup>99</sup> and while some studies have documented improvements in attention<sup>113–115</sup> in such patients, others have not.<sup>99</sup> Some evidence exists of cognition-enhancing effects in healthy elderly people<sup>116</sup> and improvements in attention for elderly people with memory impairment.<sup>117</sup> Improvements in psychomotor performance in healthy volunteers are larger in smokers than in non-smokers, probably due to the offsetting of withdrawal effects.<sup>118</sup> The abuse potential of pharmaceutical nicotine is thought to be low.<sup>1</sup>

Excitatory aminoacids*D-cycloserine and glycine*

The antituberculosis antibiotic<sup>93</sup> D-cycloserine acts as a partial agonist at the glycine-binding site on NMDA receptors to enhance glutamate signalling. A Cochrane review of two of the four studies of D-cycloserine for AD found no benefits.<sup>100</sup> Only one other small trial reported benefits.<sup>119</sup> The authors attribute this short-term finding to the use of higher doses (100mg/day) than in other trials.

Research on D-cycloserine includes the finding that 15mg can reverse scopolamine-induced amnesia in healthy people.<sup>120</sup> Subsequently, a trial of biologically available glycine found improvements in episodic memory in young students and middle-aged men. The latter group also sustained benefits to attention.<sup>121</sup> These findings may provide the rationale for the unproven suggestion that trimethylglycine is a cognition enhancer.

Related agents have also been investigated for cognitive decline in schizophrenia, together with newer generations of antipsychotics (so-called 'atypical' antipsychotics).<sup>122-126</sup> It is suggested that atypical antipsychotics act on NMDA receptors in addition to monoamines, which could explain why these agents might preserve cognition more than classic antipsychotics that antagonise dopamine. However, the extent to which these agents preserve cognition is debated.<sup>127,128</sup> Atypical antipsychotics increase the risk of stroke in people with dementia, although this risk may be small.<sup>129,130</sup>

### *Memantine*

This moderate-affinity NMDA antagonist may prevent neurotoxicity due to overactivity of excitatory aminoacids such as glutamate, and thus enhance learning and memory. A Cochrane review of memantine for dementia found significant broad benefits in moderate-to-severe AD, vascular dementia and combined or non-specified dementia, though some effects were modest.<sup>101</sup> Adverse effects were low, and the authors conclude that more studies are needed. Subsequently, an RCT has found memantine beneficial when added to donepezil.<sup>131</sup> Memantine is licensed in the UK for moderate-to-severe AD and is usually well tolerated,<sup>93</sup> although hallucinations are occasionally reported.

Little evidence exists for the effects of memantine on cognition in healthy volunteers, although the drug can impair conditioned behaviours in humans and animals,<sup>132-134</sup> suggesting potential for use in addiction. However, one report suggests that the drug may have mild subjective stimulant effects.<sup>133</sup>

### Calcium channels

#### *Calcium-channel blockers*

Calcium influx into neurons occurs via both NMDA channels and voltage-dependent calcium channels – excessive calcium influx can cause neurotoxicity. Thus, calcium-channel blockers have been investigated for effects on cognition, effects on blood flow and also on voltage-dependent calcium channels, which assume greater importance with ageing.<sup>37</sup> A Cochrane review of nimodipine in dementia reviewed nine of 14 possible trials.<sup>102</sup> Pooled data indicated benefit on various scales including cognition but not on functioning. Nimodipine and related drugs, but not nitrendipine,<sup>47</sup> are licensed in the UK for hypertension treatment.<sup>93</sup> Pre-clinical and animal research also indicate benefits from nimodipine and nivaldipine.

### Adenosine and phosphodiesterase

Cell signalling by cyclic AMP [cAMP] is important in various types of LTP. Inhibition of phosphodiesterase particularly type 4, which breaks down cAMP, can increase cAMP signalling, while antagonism at adenosine receptors acts indirectly to inhibit phosphodiesterase. AD pathology may in part depend on blocking cAMP signalling.<sup>135</sup> Thus, cognition is potentially enhanced by

adenosine antagonists such as caffeine, and by phosphodiesterase inhibitors, both non-specific (e.g. papaverine and propentofylline) and specific (e.g. rolipram).

### *Caffeine*

The role of the world's most popular drug as a cognition enhancer is a longstanding controversy. Experimental data indicate that caffeine can enhance the turnover of central noradrenaline in low arousal states, and may have cholinergic actions.<sup>136</sup> However, recent data suggest that caffeine only enhances cognition in caffeine-dependent people in withdrawal e.g. after a 6–8-hour sleep.<sup>137,138</sup> High doses can cause side-effects in vulnerable people while caffeine withdrawal involves headaches and tiredness.

### *Propentofylline*

This phosphodiesterase inhibitor also blocks adenosine uptake, and has other actions including NGF secretion. Nine RCTs have been conducted in people with various types of dementia but five (n=1,200) remain unpublished.<sup>103</sup> Thus, a Cochrane review considered only four RCTs but did find limited evidence of benefit on cognition and functioning.<sup>103</sup> However, the application for European licensing for this agent was unsuccessful.

### *Rolipram*

This selective type-4 phosphodiesterase inhibitor enhances long-term retention of contextual learning.<sup>139</sup> In addition, it corrected learning deficits in a mouse model of a congenital syndrome associated with impaired cognition.<sup>140</sup> Rolipram is licensed in some European countries and Japan, though not the UK, as an antidepressant.

## Monoamines

The monoamine neurotransmitters – dopamine, serotonin, and noradrenaline – have substantial and complex effects on cognition. The interaction of dopamine and glutamate can promote LTP and LTD in various brain regions.<sup>141</sup> Dopamine neurotransmission, which is important for motor function and cognition, declines with age and these age-related decreases may contribute to impaired attention and mental flexibility plus other deficits.<sup>142</sup> Dopamine D2 receptors appear important for verbal learning and executive function,<sup>143</sup> while D1 receptors are implicated in spatial working memory.<sup>144</sup>

Serotonergic projections modulate various aspects of learning and memory.<sup>21,22,145</sup> However, the contribution of the 14 receptor types<sup>22</sup> plus indirect effects due to cortical modulation of other monoamines is complex.<sup>146</sup> Serotonin appears to modulate the impact of dopamine upon spatial working memory<sup>147,148</sup> and attention,<sup>149</sup> while serotonin alone appears to modulate declarative memory.<sup>148</sup>

Drugs that act via noradrenaline can have cognition-impairing or enhancing effects,<sup>150,151</sup> perhaps due to the complex cortical interaction between noradrenaline and dopamine.<sup>152</sup> Some agents that enhance noradrenergic function might act as stimulants directly, or indirectly by increasing cortical dopamine. States that involve increased noradrenergic activity have been linked with enhanced emotional memory formation (e.g. post-traumatic stress disorder) and impaired working memory.<sup>151</sup>

### *Methylphenidate*<sup>1</sup>

Methylphenidate is the cognition enhancer with the best evidence base, improving various aspects of cognition in children and adults with ADHD.<sup>153,154</sup> The short- and long-acting preparations licensed for ADHD<sup>93</sup> work by reducing dopamine uptake into neurons via the dopamine transporter. Guidance from the UK's National Institute for Clinical Excellence recommends that such treatments be used after remedial measures have been tried.<sup>155</sup> However, large RCTs report little benefit from such support, whether alone or in addition to medication.<sup>156,157</sup> One concern over long-

term psychostimulant treatment is the potential to mildly restrict growth, perhaps due to appetite suppression.<sup>158</sup>

In people with ADHD, the abuse potential of this psychostimulant is low.<sup>159,160</sup> Indeed, appropriate treatment in childhood is linked with reduced substance misuse later.<sup>161</sup> However, methylphenidate can be abused if it is administered via routes that provide rapid increases in blood levels.<sup>162</sup> New formulations are designed to prevent such abuse. A trend has developed for healthy students and others to take methylphenidate as a cognition enhancer, particularly for situations like exams. Studies have reported improvements in working memory in young adults, which have been linked with changes in cerebral blood flow.<sup>163,164</sup> However, other evidence suggests a lack of effect in elderly men and young sleep-deprived volunteers.<sup>165,166</sup> Its use has been explored in pilot studies for HIV-associated cognitive slowing, post-stroke recovery, and traumatic brain injury.

### *Amphetamines<sup>1</sup>*

Amphetamines, including dexamphetamine sulphate and mixed amphetamines, are psychostimulants with efficacy in ADHD.<sup>93,153,154</sup> In addition, amphetamines are reported to enhance several cognition measures in healthy volunteers, including response speed<sup>167</sup> and retention and recall of verbal memory,<sup>168</sup> with variable effects on accuracy of responding. Amphetamines act indirectly to prompt release of dopamine, are linked with synaptic plasticity,<sup>169</sup> and thus may help with cognitive decline. Such agents have been used by various armed forces for years. However, a major problem with rapid-acting dopamine agonists is the potential for abuse. Outside certain contexts, amphetamines can lead to dependency, and may cause neurodegeneration and psychosis.<sup>1</sup>

### *Other dopaminergic agents, including antipsychotics*

In general, dopamine antagonists such as the classic antipsychotics (e.g. haloperidol<sup>167</sup>) act to impair working memory and other aspects of cognitive function, while agents that promote dopaminergic actions, especially at D1 receptors,<sup>144,170</sup> act to enhance working memory. D1 agonist effects may be particularly important to reverse cognitive deficits in schizophrenia.<sup>170</sup> Agents with dopamine agonism include bupropion and the selective D2 agonist bromocriptine. D2 receptors are thought to be involved in executive functions, such as planning, which explains some reported effects of bromocriptine.<sup>171</sup> However, studies in healthy volunteers found that the drug impaired some aspects of executive function but improved spatial memory.<sup>172</sup> Another study found effects on working memory were inversely related to baseline function,<sup>173</sup> a frequent finding with psychostimulants.

Selegiline inhibits the breakdown of dopamine by monoamine oxidase A and has been studied in PD and AD. A Cochrane review found some benefit of selegiline in AD plus good tolerability. However, benefits seemed unlikely to be clinically meaningful.<sup>104</sup> Use in PD together with levodopa has been linked with increased mortality and falls.<sup>174</sup> Selegiline might be useful for HIV-associated cognitive decline.<sup>175</sup>

### *Atomoxetine*

Atomoxetine is a novel treatment for ADHD<sup>93</sup> that acts as a noradrenaline reuptake inhibitor to indirectly enhance cortical dopamine levels. It is generally well tolerated in children and adults. Abuse potential has not been reported, and monkeys do not reliably self-administer the drug, unlike methylphenidate.<sup>176</sup> Reboxetine is a similar agent that is licensed for depression.<sup>93</sup>

### *Antidepressants and anxiolytics*

Treatment with selective serotonin-reuptake inhibitors (SSRIs) has been linked with performance enhancement, with vigilance impairment, and with no effect on cognition.<sup>177-179</sup> These discrepancies may be explained by differing SSRI actions on neurotransmitters other than serotonin

(5HT). For example, sertraline, which has additional dopaminergic activity, causes no vigilance impairment, in contrast to citalopram, which has the greatest serotonergic activity.<sup>178</sup> These drugs and similar agents that work additionally or exclusively via noradrenaline may also enhance mood-congruent memory recall.<sup>180</sup> Reports from animal studies that 5HT3 antagonists, such as ondansetron, might enhance cognition have not been validated in humans.<sup>181</sup>

In people with schizophrenia, agents like tandospirone that activate 5HT1A receptors are linked with improved memory.<sup>182</sup> However, the fact that 5HT1A binding releases dopamine in the prefrontal cortex has led some authors to suggest that 5HT1A-binding drugs, including atypical antipsychotics, act to enhance cognition via dopaminergic mechanisms,<sup>183</sup> particularly the latest agents, aripiprazole, a dopamine partial agonist, and ziprasidone, a D2 antagonist.

#### *Other noradrenergic agents*

Brain adrenoreceptors are implicated in arousal and attention, and the impact these have on sensory processing and memory, especially emotional and working memory.<sup>150,151</sup> Thus,  $\alpha_2$ -receptor agonists (e.g. clonidine, guanfacine) improve, whereas  $\alpha_1$ -agonists impair, working memory, perhaps in a similar fashion to high noradrenergic states like stress. Further,  $\alpha_1$ -agonists and  $\beta$ -receptor antagonists impair formation of emotional memory, particularly during memory review, which has led to the hope of using agents such as  $\beta$ -blockers for selective forgetting of traumatic memories.

#### Other stimulant pathways

##### *Modafinil*

Modafinil is a novel wakefulness-promoting agent of unknown mechanism. It is licensed in the UK to treat excessive daytime sleepiness associated with narcolepsy, sleep apnoea, and other conditions such as shift work,<sup>93</sup> and has good reported tolerability. Anecdotal reports suggest off-label use of the agent by students, pilots and military personnel, among others. Small studies suggest that modafinil has benefits for ADHD in children<sup>184</sup> and adults,<sup>185</sup> and in schizophrenia.<sup>186</sup> Most reports<sup>187,188</sup> but not all<sup>189</sup> suggest that modafinil moderately enhances cognition in healthy volunteers, in addition to effects on alertness. Various lines of evidence suggest low potential for abuse.<sup>190</sup> Adrafinil is a little-studied related compound.

#### Cerebral metabolism and blood flow

Modern brain-imaging techniques<sup>5</sup> demonstrate that conscious effort is underpinned by increases in cerebral metabolism and blood flow. Vasodilator agents like naftidrofuryl have been proposed to enhance cognition. Vascular dementia was thought to be the main condition that might respond to cerebral vasodilators, but impaired blood flow may occur in other disorders. Several other cognition enhancers have at least partial actions on these diffuse processes, including phosphodiesterase inhibitors and calcium-channel blockers. Other agents include the pyrrolidinones (racetams), ergot alkaloids, and vinpocetine, although these have additional mechanisms.

##### *Naftidrofuryl*

Naftidrofuryl is licensed in the UK as a peripheral vasodilator,<sup>93</sup> and is prescribed for dementia in several other countries. Even as an oral medication, side-effects, including hepatitis and liver failure, may limit its use. A Cochrane review of its use for cognition enhancement is planned.<sup>191</sup>

##### *Pyrrolidinones*

Many pyrrolidinone derivatives are available worldwide, including piracetam, oxiracetam, aniracetam, nefiracetam and levetiracetam. Piracetam was the first reported nootropic agent. Since then, racetams have been studied in and used for several disorders, including dementia, post-concussion syndrome, post-surgical neuroprotection, alcohol-related cognitive impairment, and

dyslexia. Piracetam is currently prescribed in several European countries for cognitive impairment, including dementia, and is approved in the UK for adjunctive treatment of myoclonus.<sup>93</sup> Levetiracetam has recently been approved in the UK for adjunctive treatment of partial epilepsy.<sup>93</sup> Nefiracetam is in clinical trials for dementia and post-stroke treatment.

Many trials have been done of piracetam, although a Cochrane review of piracetam for dementia or cognitive impairment excluded several of these on methodological grounds.<sup>105</sup> The remainder had inconsistent results, although overall, piracetam carried around three-fold odds of improvement compared with a placebo. Levetiracetam has potent antiseizure activity so this agent may preserve cognition in people with epilepsy.<sup>192</sup> The racetams are reported to have good tolerability.

Actions of piracetam include enhancement of brain metabolism and neuroprotection.<sup>105</sup> At higher doses, the agent may be antithrombotic. Nefiracetam binds to GABA-A, and potentiates activity at NMDA and acetylcholine nicotinic receptors, and aniracetam acts via acetylcholine and glutamate.

### *Ergot derivatives*

Derivatives of natural ergot alkaloids such as hydergine (co-dergocrine – a mixture of four ergoloid mesylates) and nicergoline have been used for decades in dementia and age-related cognitive impairment, as well as for arterial hypertension and insufficiency.<sup>106,107</sup> Hydergine is approved in the UK as an adjunct in elderly patients with mild-to-moderate dementia<sup>93</sup> and is licensed in the USA for idiopathic mental decline.<sup>106</sup> Nicergoline is available in some 50 countries, but not the UK, for treatment of vascular disorders, including cerebrovascular disease.<sup>107</sup>

An updated Cochrane review with a meta-analysis of 12 trials found an overall significant benefit of hydergine for dementia symptoms.<sup>106</sup> Some inconsistencies between trials may be due to the dose and the duration of therapy. Benefit may be evident mainly for younger patients and those with vascular dementia. Some evidence exists for limited benefit in people with mild memory impairment and healthy elderly. Tolerability is generally good.

A Cochrane review of 14 trials of nicergoline found generally consistent results in its favour, although the benefits were not always statistically or clinically significant.<sup>107</sup> In one trial with electroencephalogram (EEG) outcomes, nicergoline was found beneficial for both multi-infarct and Alzheimer-type dementia, and resulted in EEG indicators of enhanced vigilance and increased cognitive processing. The drug has also been found useful in elderly hypertensive patients with white-matter changes on brain scanning but no dementia.<sup>193</sup>

Ergot alkaloids have marked effects on blood flow, which were originally thought to be the main mechanism of action. However, more complex actions, including neurotransmitter changes, are reported.<sup>106</sup> Nicergoline might also have antioxidant and neurotrophic actions.<sup>107</sup>

### *Vinpocetine*

Vinpocetine was synthesised from apovincamine, an alkaloid in *Vinca minor*. Clinical studies report selective enhancement of cerebral blood flow and metabolism, including enhanced glucose uptake, which may protect against the effects of hypoxia and ischaemia.<sup>194,195</sup> Non-clinical studies also suggest raised intracellular energy storage, neuroprotectant and anticonvulsant activity, phosphodiesterase inhibitor action and reduced platelet aggregation.<sup>108</sup>

These promising studies have not been supported by good-quality RCTs. A Cochrane review identified only three studies totalling 583 people, which showed some benefits. However, few patients were treated for more than six months, hence the conclusion that the evidence does not support clinical use.<sup>108</sup> Vinpocetine is not licensed in the UK. It is probably well tolerated.

### Neuroprotection and neural growth

Several cognition enhancers are thought to work at least in part by protecting the brain from

damage,<sup>196</sup> e.g. due to oxidation, free radical damage or neurotoxicity. Agents that act through such mechanisms include memantine, melatonin, idebenone, cerebrolysin and potentially some endogenous neuropeptides and analogues. The secondary release of neurotrophic factors, such as NGF and BDNF, is a key action of phosphodiesterase inhibitors, among others.

#### *Idebenone and coenzyme Q10*

Idebenone, a synthetic analogue of coenzyme Q10, is thought mainly to reduce oxidative damage, perhaps even in normal ageing. In particular, idebenone protects cell membranes and mitochondria and the latter also helps preserve energy storage.<sup>197</sup> It also promotes release of NGF, together with other proposed actions,<sup>198</sup> including effects on monoamine turnover.<sup>199,200</sup> A Cochrane review of idebenone was planned but is withdrawn currently. Several RCTs and two open studies have been reported in various populations, including mixed disease. Most are small and of limited duration, and findings are contradictory. This agent is not licensed in the UK. Tolerability is thought to be good. Coenzyme Q10 is available as a dietary supplement but has not been studied for efficacy in humans.

#### *Cerebrolysin*

Cere (cerebrolysin) is a mixture of peptides and aminoacids derived from purified pig brain proteins. This intravenous preparation has been evaluated in various RCTs, mainly for AD, which show persistence of cognition improvement beyond the treatment period.<sup>201-204</sup> These appear to confirm pre-clinical suggestions of neurotrophic action but a systematic review is awaited.<sup>205</sup>

#### *Endogenous neuropeptides and analogues*

Numerous small proteins are found in the brain – these neuropeptides have complex and multiple actions, and may act as hormones, neurotransmitters and local messengers. A role in cognition, including neuroprotective effects, has been proposed for vasopressin, somatostatin, growth hormone, insulin-like growth factor-1, neuropeptide Y, orexins, vasoactive intestinal polypeptide, glucagon-like peptides, galanin, nociceptin/orphanin FQ, pro-opiomelanocortin derivatives, TRH (thyrotropin-releasing hormone), and others. Thus far, inconclusive clinical research has been mostly limited to studies on vasopressin and analogues (e.g. desmopressin). Long-term vasopressin treatment did exert a modest effect on attention in healthy elderly,<sup>206</sup> while short-term memory improvement is reported in children taking desmopressin for bedwetting.<sup>207</sup>

#### Miscellaneous agents

The antidepressant tianeptine prevents and reverses the adverse effects of glucocorticoids and stress on dendritic changes and synaptic plasticity, brain morphology, and memory.<sup>27,208</sup> Although a serotonergic action was assumed, tianeptine might act to protect neurons from excessive actions of excitatory aminoacids.

The putative cognition enhancer Gerovital H3 contains procaine, a local anaesthetic related to the psychostimulant cocaine,<sup>1</sup> and other ingredients that produce para-amino-benzoic acid and diethylaminoethanol in the body. One reported action is increased production of choline, though many other actions, including monoamine-oxidase inhibition, are claimed. The related dimethylaminoethanol (DMAE) is marketed as a dietary supplement.

CDP-choline (citicholine) is thought to accelerate resynthesis of membranes and suppress damaging release of free fatty acids. CDP-choline is licensed as a drug in several European countries, but not the UK. The Cochrane review of CDP-choline suggests positive effects on memory and behaviour in populations with mixed cerebral disorders, such as cerebrovascular disease.<sup>109</sup> The authors suggest that further research needs to focus on longer-term studies in populations with well-defined disorders.

## **Cognition enhancers in development**

The following overview of developmental drug leads includes drugs at clinical trial stage<sup>209</sup> and some that have shown promise in pre-clinical tests and animal models, although the latter information is not comprehensive due to variations between companies in publishing practices. Findings in animal models and pre-clinical studies do not reliably translate to effects in humans, and the likelihood is that most of these agents will be abandoned due to inefficacy or intolerable side-effects. However, the approaches detailed seem likely to be pursued.

### Glutamate

Many companies are developing agents that act on glutamate via NMDA and AMPA receptors. Effects are thought to encompass increased synaptic plasticity, compensation for loss of glutamate signalling in disease and normal ageing, and increased production of neurotrophic factors such as BDNF. Compounds that alter glutamate signalling are under investigation for PD, dependency and addiction, anxiety, schizophrenia, and pain.

Ampakines (e.g. Ampalex) and related agents potentiate the action of AMPA receptors to increase LTP. They might also be neuroprotective. Results in rodent models and in early clinical trials have been generally positive. Ampalex is currently in a phase-II clinical trial for AD and has completed phase-II studies for MCI.<sup>210</sup> Other AMPA-targeted agents are in development.<sup>211,212</sup> Several NMDA antagonists have been developed. CP101606 is in phase II trials for head injury and NPS1506 is in phase I trials for prevention of ischaemic damage due to head injury and stroke.

Other potential targets to influence glutamate signalling are metabotropic receptors, which act in a different manner from other glutamate receptors.<sup>213,214</sup> One concern over this and other glutamatergic targets is the possibility that excess stimulation could cause neurotoxicity, seizures or hallucinations. A large clinical trial of a potential anti-anxiety agent targeted at metabotropic glutamate receptors was halted after rodents developed seizures on the drug.<sup>214</sup>

### Calcium channels

Various calcium channels are implicated in synaptic plasticity, particularly with ageing, while excessive calcium flow into neurons leads to neurotoxicity. MEM1003, which modulates calcium flow into cells, began phase I testing in healthy volunteers in 2003,<sup>215</sup> while final data could be available before 2008 if the drug reaches phase III testing for dementia and MCI.<sup>216</sup>

### Maxi-K channels

Opening of maxi-K channels (potassium M-channels) controls the excitability of neurons due to excess calcium.<sup>217</sup> Agents that open these channels have potential for neuroprotection and treatment of epilepsy (e.g. retigabine). Despite promising results from phase I and II trials, BMS204352 failed to demonstrate superior efficacy over placebo in a phase III trial for acute stroke. Other agents have been identified that show promise in pre-clinical studies.<sup>217</sup>

### CREB and phosphodiesterase

The protein CREB responds to increasing levels of cAMP in the cell to promote events involved in LTP,<sup>218</sup> and may act as a switch to turn newly acquired knowledge into long-term memory.<sup>219</sup> At least two companies are working on type-4 phosphodiesterase inhibitors, which increase levels of cAMP and thus indirectly enhance the action of CREB. MEM1414<sup>215</sup> has started phase I clinical trials while HT0712<sup>220</sup> has been extensively tested in animal models. A future target might also be the suppression or antagonism of the CREB repressor protein.

### Acetylcholine

Many new compounds in development target acetylcholine. The cholinesterase inhibitor phenserine, which also may reduce toxic  $\beta$ -amyloid,<sup>221</sup> is in human trials, as is the combined cholinesterase inhibitor and monoamine oxidase inhibitor ladostigil, which may have neuroprotectant, antidepressant, and cognition-enhancing properties.<sup>222,223</sup> Other approaches to increase cholinergic neurotransmission include choline uptake enhancers (e.g. MKC231) and cholinergic agonists, which stimulate nicotinic and muscarinic receptors. MKC231 represents a new class of agent thought to reverse cholinergic deficits. It also offers protection against calcium-induced neurotoxicity.<sup>224</sup> The agent showed some improvement in cognitive performance in early human trials, and is currently in phase IIb trials for AD.<sup>225</sup>

Several nicotinic agonists have been developed with the aim of increasing cognition-enhancing properties and reducing the side-effects of nicotine. ABT098 showed neuroprotectant and some cognitive-enhancing properties,<sup>226,227</sup> but does not seem to have been developed further. GTS21 has shown promising results in animal models<sup>228</sup> and phase I clinical studies.<sup>229</sup> Newer promising leads include TC1734, SIB1553A, and MEM3453. Another theoretical approach to increasing cholinergic transmission is the stimulation of muscarinic receptors, especially with M1 agonists, although evidence on agents such as talsaclidine,<sup>230,231</sup> xanomeline and sabcomeline suggests that this approach is not useful in humans.

### Dopamine

Extensive research has led to various developmental drugs focused on altering dopaminergic neurotransmission, especially for cognition improvement in PD. Treatment of this low-dopamine state improves cognition and motor function, but also alters outcome-related learning,<sup>232</sup> hence the importance of this neurotransmitter in drug dependence.<sup>1</sup> The new monoamine-oxidase-B inhibitor rasagiline, which may also be neuroprotective, is in late clinical trials for AD and awaiting approval for PD.<sup>233</sup> Another strategy involves inhibition of monoamine reuptake, for example, by NS2330, an agent that increases levels of dopamine, noradrenaline and acetylcholine, which is in phase II trials for AD.

Stimulation of dopamine receptors might lead to long-term improvements in cognition, due to the phenomenon of sensitisation – an increase in sensitivity of the stimulated receptor.<sup>234</sup> Full and partial dopamine agonists include pibedil, BP897, and ABT431,<sup>1</sup> plus sumanirole, which is in phase II trials for PD. Drugs that rapidly enhance dopamine release may have abuse potential.<sup>1</sup>

### Serotonin

Binding to specific serotonin receptors might help improve cognition in neurodegenerative disease and in schizophrenia, possibly via changes in other neurotransmitters.<sup>235</sup> For example, 5HT6 antagonism can increase levels of acetylcholine, glutamate, dopamine and noradrenaline.<sup>236</sup> The 5HT6 antagonist SB742457 is in phase I trials for AD. Another drug, SL650155, a partial agonist at 5HT4 receptors, is in phase II trials for cognitive impairment and dementia.<sup>237</sup> 5HT1A agonists and 5HT2A antagonists might also impact on cognition. Xaliproden is a 5HT1A agonist that also mimics the action of NGF. It is in phase II trials for AD and neuropathy.

### GABA

Several companies have agents in development that turn off GABA neurotransmission by partial inverse agonist action at the benzodiazepine receptor binding site. These agents are hoped to produce cognition-enhancing effects without adverse effects such as anxiety – e.g. PCALC36.<sup>238</sup> SB737552 (S8510) is in phase I trials for AD and vascular dementia. NS105 is a newer lead that appears to increase cholinergic neurotransmission and inhibits GABA-B receptor binding.<sup>239</sup>

### The cannabinoid system

The extensive endocannabinoid system probably modulates learning by transmitting signals from

post-synaptic neurons to cause pre-synaptic effects, such as synaptic weakening.<sup>240</sup> Rimonabant (SR141716A) is currently under study for reduction in cravings<sup>1</sup> such as in smoking and to treat obesity. This and other cannabinoid-1 receptor antagonists have shown benefits in memory consolidation and might counteract the amnesic effect of  $\beta$ -amyloid in AD. However, the increased strength of memory formation might act as a source of interference when memory needs to change dynamically, indicating a trade-off in cognitive effects.<sup>241</sup> Dexanabinol, a synthetic cannabinoid, is in phase III trials for neuroprotection after traumatic injury, and phase II trials for neuroprotection during cardiac surgery. However, its main mechanism of action may be weak NMDA antagonism.

### Histamine

Histamine-3 receptors inhibit release of several neurotransmitters involved in cognition. The histamine-3 antagonist A349821 increases histamine release and has shown cognition-enhancing properties in rodents.<sup>242</sup>

### Neurohormones and neuropeptides

Interventions that promote or reduce activity of the multitude of hormones and peptides that act as neurotransmitters offer diverse potential strategies to enhance cognition, including receptor-binding agents, peptide releasers and synthetic peptides that mimic endogenous neuropeptide function or downstream targets. High, persistent circulating levels of glucocorticoids can impair memory functioning, so a current trial of mifepristone will determine whether antagonism of glucocorticoids can slow decline in AD.<sup>243</sup> Notably, inhibition of  $11\beta$ -hydroxysteroid dehydrogenase with carbenoxelone improves cognition in healthy elderly and cognitively impaired people.<sup>244</sup>

NC1900 is an analogue of vasopressin that can enhance spatial memory, probably by acting on a specific receptor on cholinergic neurons.<sup>245</sup> FK960 appears to enhance cerebral blood flow through release of somatostatin<sup>246</sup> but was not effective in humans. NAP, a peptide derived from a protein released by vasoactive intestinal polypeptide has neuroprotectant properties.<sup>247</sup> S17092 inhibits an enzyme that breaks down neuropeptides and showed promise in pre-clinical and clinical studies, but was abandoned after phase I studies.<sup>248</sup> Synthetic ligands have been developed including C3d, which binds to neural cell adhesion molecule,<sup>249,250</sup> and FG loop, which binds to fibroblast growth factor (FGF) receptor-1.

### Other molecular targets

Several other strategies are under investigation, which mainly target disease processes associated with neurodegeneration. It is unclear whether any of these approaches will prove useful for cognition enhancement in other scenarios. However, those that target molecular messengers involved in cognitive processes inside neurons might prove useful in states other than neurodegeneration, such as agents acting on the protein kinase C that modulate effects of stress on working memory.<sup>251</sup>

CEP1347 and AS601245 inhibit certain protein kinases – the latter neuroprotectant is in phase III trials for PD.<sup>252</sup> CPII 189 inhibits the potentially damaging immune chemical tumour necrosis factor- $\alpha$  and is in phase II trials for AD. One key strategy aims to mimic or enhance the activity of neurotrophic factors such as NGF, glial-cell-line-derived neurotrophic factor, and neuroimmunophilin ligands<sup>253</sup> (e.g. GPII485<sup>254</sup> for PD). One action of antidepressants is proposed to be neural growth due to release of neurotrophic factors like BDNF and FGF.<sup>13,255</sup>

One example of agents that are probably selective for disease modification is in the development of several strategies to inhibit amyloid formation in AD, which depends on the breakdown of amyloid precursor protein by  $\beta$ - and  $\gamma$ -secretase enzymes. R-flurbiprofen lowers levels of  $\beta$ -amyloid, perhaps by altering secretase activity,<sup>256</sup> and is in phase II testing. This drug is of interest since it is one stereo-isomer (mirror-image) of the two found in the known drug flurbiprofen, in which R-

flurbiprofen has markedly different properties from the anti-inflammatory L-flurbiprofen. Thus, any benefits of anti-inflammatory agents in dementia might at least partly be due to other mechanisms. Secretase inhibitors are under development but agents that target such ubiquitous substrates might be limited by systemic toxicity.<sup>256</sup> Other agents that target  $\beta$ -amyloid in AD include Alzhemed, a glycosaminoglycan in phase III trials and AAB001, a monoclonal antibody in early human trials.

### Genome and stem cells

The potential is immense for therapeutic strategies that target the genome, use cell replacement, or both.<sup>257–259</sup> In the next two decades, science in this area is likely to make major advances, although few successful therapies are expected given the poor success rate over the past decade or so. Two current approaches are in phase I trials of patients with AD, who are treated either with their own re-implanted skin cells engineered to carry the NGF gene, or with a virus to deliver the gene directly into the body.<sup>260</sup>

Various strategies are under study to use stem cells to replace dead neurons in neurodegenerative disease. Early clinical trials have been done for PD and traumatic brain injury, while therapy for stroke and other disorders is proven in animal models.<sup>258,261–263</sup> Difficulties with administration and unknown long-term effects mean that such strategies are unlikely to be employed for cognition enhancement for non-medical purposes, at least for a long time.

### **Future cognition enhancers**

Several trends will impact on the future development and use of cognition enhancers:

#### *Changes in society*

In the UK, moderately effective treatments for some neurodegenerative diseases are already available. These and other treatments are likely to impact on quality and length of life. The increased adoption of such strategies, and the development of new approaches to disease modification and cognition enhancement, will likely occur in the context of increasing longevity, which could further enhance the market for such interventions. In turn, drugs and other strategies that halt, prevent or reverse ageing processes, including cognitive impairment and age-related diseases, could perpetuate this cycle, in which a relatively healthy and wealthy elderly population seek to further lengthen lives lived in good health.

#### *Increasing knowledge*

Scientific research is likely to continue to expand our knowledge of the mechanisms underlying cognition and their impairment in disease and normal ageing. Promising new avenues for disease-modifying drugs are being explored in the laboratory and in clinical trials. In addition, many people are conducting long-term self-experimentation by taking agents purported to be cognition enhancers. These trends will inform development of better agents and non-drug strategies that work via similar or novel mechanisms, though only modest effects are anticipated in the near future.

Comparative work may indicate an overlap between brain disorders and also with psychiatric diseases. Research on the mechanisms of disease-modifying and cognition-enhancing interventions could reveal agents that cross over for use in other conditions. For example, the MATRICS initiative to support development of drugs to treat cognitive deficits in schizophrenia<sup>264</sup> may uncover drugs for use in other conditions, particularly those characterised by similar frontal cortical dysfunction. Strategies to screen known agents for novel properties might be similarly fruitful – recent highlights include potential effects of certain antibiotics for neuroprotection<sup>265</sup> and antiepileptics for longevity.<sup>266</sup> Cognition enhancers for healthy people will be developed with the aim of targeting known and new substrates of normal cognition. There is also potential for

interventions that act in more global ways. Possibilities include widely enhancing neural connectivity and facilitating the recruitment of other brain regions for specific functions.

Changes in pharmacological technologies, including high throughput screening for potential drug candidates, nanotechnology and rational drug design, may increase the pace and success rate of drug development. Genomic and proteomic techniques seek to identify large numbers of cellular changes in genetic 'messages' and protein products, respectively. They seem likely to provide insights into mechanisms of and variance in both pathology and drug actions.<sup>267,268</sup> Such knowledge is already starting to inform the development of biomarkers and drugs.<sup>269,270</sup>

Advances in technologies to image the living brain and the combination of imaging techniques will expand our knowledge of cognitive processes, and could assist the targeting of therapies, at least in disease states.<sup>5</sup> The nascent field of pharmacogenomics could allow treatments to be tailored to the genetic make-up of an individual, although an individual's future degree of cognitive impairment is likely to be much more difficult to predict.<sup>4</sup> Development of biomarkers for early brain changes in ageing and disease could allow early intervention and an emphasis on a preventative approach to cognitive decline.

### *Scientific limitations*

Years of research on learning and memory have not yet translated into highly effective disease-modifiers or cognition enhancers. One major impediment is the lack of good animal models and the consequent failure to translate findings in animals to efficacy in humans. Future developments seem likely to be more rapid for disease-modifying drugs than for mechanism-based cognition enhancers for healthy people. Already, transgenic animal models of AD have revealed potential pathways to new treatment strategies, although for other disorders, the genetic origins are much less clear and likely to be more complex. If similar animal models could be developed for other cognitively impairing neuropsychiatric diseases, progress could be markedly enhanced.

Strategies already exist for the rapid production and screening of transgenic animals for effects on cognition. Now robotic techniques have been developed to reduce the number of animals required and the screening times.<sup>271</sup> Invertebrate models are an alternative strategy.<sup>270</sup> In all cases, however, difficulties exist with the development of suitable tests to document the effect of gene mutations on cognition.<sup>272</sup> Thus, the translation of such effects to humans remains an uncertain science. Commercial priorities mean that the extent of industry failures – compounds that enhanced learning and memory in animals but had no effect on humans, or had unacceptable side-effects – is not known, though some are reported.

In human studies, no biomarkers have yet been widely accepted even for AD, which raises the question of how to decide who should receive disease-modifying drugs. Moreover, we do not yet know how to accurately measure the full effects of drugs on cognition, nor do we know the most relevant indicators to predict desirable outcomes from therapies, such as maintaining independent living or reduced admission to nursing homes. The uncomfortable fact remains that despite huge research efforts, we do not yet know how to substantially enhance cognition in humans.

## **Implications**

If effective cognition enhancers are developed, our capability to use them in the best way for individuals and society depends on several factors, mainly potential benefits and harms, plus ethical and social aspects of their use. The latter concepts have recently been reviewed.<sup>273–278</sup> However, the social and ethical frameworks in which cognition enhancers could be used in the future will impact on their benefits and harms, and so are briefly discussed here.

### *Potential benefits and harms*

Cognition-enhancing technologies are likely to have three potential applications: disease states; MCI and normal ageing; and healthy cognition. In the cases of the first two applications, interventions may be useful for halting, preventing and reversing cognitive decline. The benefits to society of reductions in disease-related impairments and enhancements in human cognitive capabilities could potentially be enormous. Other benefits seem likely, including increased knowledge of human cognitive neuroscience and interventions that benefit other conditions.

However, for people with brain disease, treatments that halt cognitive decline and lengthen life without improving its quality might be undesirable. Likewise, the prospect of halting normal ageing and the subsequent prolongation of life, if it turns out to be possible, raises dilemmas if an individual's life is of poor quality. Impacts on health and social costs plus societal effects related to an ageing population also seem likely.

One possibility is that pharmaceutical companies will not be able to deliver effective cognition enhancers within the next 20 years,<sup>279</sup> while research already suggests that the effect of cognition enhancers might be unpredictable, or vary according to baseline function, genetic make-up, gender, and other variables. Some aspects of cognition may be easier to enhance than others. If increasing memory is possible but not improved selective forgetting, cognition enhancement could lead to remembering of excess clutter and would be a liability during distressing events. 'Trade-offs' between enhancement of one function and impairment of another seem likely, and are already noted in normal brain functioning, for example, when attention on work is distracted by a need to attend to other stimuli. With cognition enhancement, one example is seen with the 'Doogie mouse' engineered to have excess NMDA receptor function, which shows increased learning ability<sup>280</sup> but might have enhanced sensitivity to pain.<sup>281</sup>

Current key concerns over harms are restricted to short-term adverse effects, although some compounds are likely to lead to dependence and have abuse potential. Few disease-modifying drugs seem likely to have abuse potential, especially if used to enhance a neurochemical deficit e.g. children with ADHD who take amphetamines. Some cognition enhancers, especially stimulant-type drugs, might show an increasing trend for abuse. Already, modafinil and other drugs are available on what is effectively a black market, and some may be abused. For people who wish to enhance cognition for non-medical purposes, the risk–benefit ratio required of a drug should be lower than that for individuals with debilitating or terminal illnesses. However, the use of putative cognition enhancers that spans decades could lead to unanticipated long-term effects. This possibility necessitates costly long-term follow-up of research participants and post-marketing surveillance.

#### *Health economics*<sup>282</sup>

If cognition enhancers are available in the future, they are likely to have substantial economic impact. The provision of disease-modifying drugs for AD alone is likely to have a marked impact on health economics. Such treatments are usually prescribed for life, and the cost of provision of such agents will depend on the source of payment and the indication. NHS treatment of dementia to restore independent living could be more cost-effective than not providing such treatments, unless this results in an increasing population of cognitively astute but physically frail elderly. The provision of disease-modifying drugs and cognition enhancers could have cost implications for Government and society in other ways: the increasing care and pension costs of an ageing society; state provision of treatments or prophylaxis for MCI and age-related deficits in otherwise healthy elderly; the regulation of over-the-counter medications; the provision of vigilance-promoting compounds for military and other state personnel; efforts to control the black market; treatment of individuals who develop dependency; and long-term monitoring of risk with extended use. Conversely, the development and marketing of effective disease modifiers and cognition enhancers is likely to represent a large growth industry, with associated economic impact.

#### *Regulation, ethics, and society*<sup>272,273</sup>

In the future, our regulatory capability will either encompass the current system of licensed prescription medicines, over-the-counter medicines, nutritional supplements and herbal medicines, or develop into new systems. Such systems could vary from regulation of all psychoactive substances to total deregulation. The former case could encompass several tiers of regulatory assessments according to likely efficacy, safety, source and availability. In the latter case, the regulatory authority could assume the role of providing independent assessment of and advice on agents, including safety alerts. MCI is a good example of how the creation of a disease label can pose diagnostic, regulatory and ethical issues.<sup>283</sup>

The widespread use of cognition enhancers could effect changes in individuals and across society. Use of such agents for purposes beyond therapy may pose ethical issues earlier than 2025 if their use becomes expected, mandated or coercive. Until recent legislation,<sup>284</sup> some US schools required children with ADHD to take medications as a condition of attendance.<sup>275</sup> In the longer term, these agents could alter inequity, but it remains an open question whether they will increase or decrease inequity, or both. The focus on aspects of ourselves as commodities is much discussed. It already happens, and the question is whether we want such trends to continue. The potential use of technologies to alter cognition in children and developing embryos presents additional technical and ethical issues.

With cognition enhancement, as with other scientific advances, a common pattern is the initial glorification of novel technology followed by demonisation as overuse ensues and adverse effects are discovered. The challenge over future cognition enhancers lies in gaining the appropriate balance in terms of individual benefits and harms, social effects, commercial prospects and public opinion.

## Conclusions

*Likelihood:* Current research is likely to bring in-depth understanding of the mechanisms that underlie cognition, including learning, memory and selective forgetting. The effects of neurodegeneration and other disease states may differ overall from those in normal ageing but there may be an impact on similar processes. Diagnosis of disease states such as dementia is likely to become more accurate and be possible earlier in the disease course.

*Future capability:* Given the increasing elderly population, cognition enhancement is likely to be increasingly required, acceptable, and desirable, for therapeutic purposes, for MCI, and for normal ageing. At the same time, the trend for healthy people to use agents for cognition enhancement for non-medical purposes seems likely to accelerate. Agents that are developed to treat neurodegenerative disorders might prove useful in other conditions, including early disease states, but will not necessarily be effective for normal ageing or for cognition enhancement in healthy people.

*Future applications:* Industry efforts to develop cognition enhancers are likely to experience unprecedented growth over the next 20 years. Research may focus separately on the treatment and prevention of neurodegeneration; modification of normal ageing processes; and enhancement beyond therapy. Each of these groups represents a large potential market.

*Likelihood:* Most societies are likely to continue to experience an increase in the number and type of putative cognition enhancers over the next 20 years. Some understanding of markers to target treatments and to predict responses seems likely to develop.

*Future capability:* A greater range of options is likely to be available for modifying the course of cognition-impairing disorders, and probably for age-related changes. Less likely but possible are

agents with large cognition-enhancing effects for use by all age groups beyond therapy. Targeting of treatments and prediction of individual responses might become possible, at least in some scenarios.

*Future applications:* More research is needed to ensure that disease-modifying drugs are used to maximise benefits and minimise harms, including on markers to guide treatment choice. The future of cognition enhancers in healthy people is uncertain but diversion and off-label use seem likely to increase. Thus, mechanisms to license or otherwise regulate cognition enhancers marketed at healthy individuals are likely to be considered.

*Likelihood:* Agents that enhance cognition are likely to have both beneficial and harmful effects, including trade-offs when enhancement of one faculty results in the impairment of another. Few agents are likely to be wholly safe, even when used by healthy people, except some dietary supplements. Few agents are anticipated to have abuse potential, although a minority, particularly stimulants, may lead to problematic use.

*Future capability:* The early effects of disease-modifying drugs and cognition enhancers are likely to be mainly predictable from their pharmacology, although a minority of immediate or early effects will be unexpected. Ongoing use of such agents could have consequences that take many decades to appear.

*Future applications:* Continued, long-term assessment after regulatory approval or other release into society of agents to enhance cognition will be important to detect later effects.

*Likelihood:* The widespread use of disease-modifying drugs and cognition enhancers is likely to have an impact on individuals and on wider society. The effects may not be restricted to enhancement of function but may also include selective impairment of functions.

*Future capability:* The increasing use of cognition enhancers for non-therapeutic purposes could impact on individual and societal concepts of intellect and intelligence, personality and personhood, although this is likely to become apparent only after effective agents have been available for several decades.

*Future applications:* The impact of cognition enhancement depends on the application. Few issues are anticipated with treatment of disease, whereas the effects on society of widespread use of effective cognition enhancers or memory erasers could ultimately be substantial. Such effects could include situations in which cognitive manipulation becomes expected, mandatory or even coercive. Cognition enhancement could become another means by which inequities in society are increased or decreased.

*Likelihood:* If current mechanisms remain, non-therapeutic cognition enhancers are likely to be regulated as drugs available by prescription from medical practitioners, or as over-the-counter preparations that are widely available. Some agents could be considered as foods, nutrients or herbal medicines.

*Future capability:* Current mechanisms are inadequate to regulate and control the expected expansion of cognition enhancement by healthy individuals, particularly online purchasing. Industry and the public will look to Government to develop effective regulatory and safety measures.

*Future applications:* Updated mechanisms are likely to be required for the most rational assessment

and control of cognition enhancement. The process might differ between agents, depending on their applications, for which different risk–benefit ratios will be acceptable. However, mechanisms to control sales via the internet seem unlikely to be fully effective. Independent safety assessment and public education (for example, on risk–benefit management) might be means by which the authorities reduce potential harms.

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No recommendation is given on reliability of websites or accuracy of content.

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