A Step Back in Time: Is There a Place for Older Drugs in the Treatment of Dementia?

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ALZHEIMER’S disease (AD) is the most feared condition associated with aging (1–3). It is a major cause of frailty and functional decline and death (4–14). In the last decade, the search for a cure has led to an exponential increase in publications on AD. In particular, research has focused on delineating the underlying pathophysiology of AD. Beta-amyloid has been demonstrated to produce memory disturbance in animals (15,16). Animal studies in transgenic mice and the SAMP8 (senescence-accelerated mouse prone 8) have strongly suggested a central role for beta-amyloid in the pathophysiology of the disease (17–25).

Other hypotheses have focused on free radical excess, mitochondrial abnormalities, and the cholinergic hypothesis (26–30). Despite the many hypotheses that have been developed, researchers remain uncertain of the exact causation of AD.

Based on the historical development of AD, and its pathophysiology, drugs for the treatment of the disease have been developed (31). At present, two major classes of drugs are used to treat AD. They are acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. Both classes of drugs have been demonstrated to be effective in animal models of AD (32,33). Based on the meta-analyses in the Cochrane collaboration database, the best of these drugs has been shown to enhance the Cognitive Global Ratings odds ratio by approximately two-fold over placebo, increase Mini-Mental State Examination (MMSE) score by 1.84 points, and increase the Alzheimer’s Disease Assessment Scale (ADAS-Cog) score odds ratio two-fold (Table 1). Recent publications on memantine have demonstrated an improvement in the severe impairment battery and activities of daily living when used alone or in addition to an acetylcholinesterase inhibitor (34,35). There are data suggesting that cholinesterase inhibitors may slow down the rate of deterioration that occurs in persons with AD (36,37). Of interest is that the meta-analysis for tacrine, the original cholinesterase inhibitor, failed to show an effect while resulting in marked hepatotoxicity (38). Thus, overall, these drugs, while clearly useful in some patients, have failed to have a dramatic effect. However, even these small effects appear to be pharmacoeconomically cost efficient (39).

With the development of these newer drugs to treat AD dementia, the potential utility of earlier drugs such as nootropics has fallen into disrepute. One of the earliest of these drugs that has been studied and used is dihydroergotoxine mesylate (DEM), or Hydergine. DEM’s mechanism in AD dementia is unknown but is thought to improve the metabolism of cerebral ganglionic cells by increasing cyclic adenosine 3′,5′-monophosphate (cAMP), increasing the uptake of water, glucose, and oxygen in cerebral cells, and stimulating vasodilatation (40,41). DEM has also been thought to modulate or affect the metabolism of serotonin and dopamine (42).

Case reports have demonstrated that patients with progressive confusion, memory impairment, disorientation, and aggressive behavior remarkably improved (less confusion, increased motivation, short-term memory improvement) after 3 months of DEM therapy at 3 mg and 6 mg doses (40,41). One of these cases further showed improvement in activities of daily living at DEM 3 mg per day (40).

In patients with clinically significant evidence of mental aging, Hydergine 3 mg per day significantly improved the severity of symptoms and intellectual function as compared to papaverine (43), even though these patients were not diagnosed with dementia. However, the symptoms listed for inclusion into the study (43) were all symptoms that are consistent with dementia. DEM at 6 mg per day demonstrated improvements in short-term memory for patients with mild dementia, but no benefit in affective or behavioral status, when compared to placebo therapy (43). Hydergine has also significantly improved cognition and functioning in patients with mild-to-moderate mental deterioration (34).

One study evaluated a different formulation of DEM as a liquid in a capsule, postulating that this dosage form would allow for greater bioavailability. However, there was no difference found between the DEM and placebo, which may have been related to the dosage form utilized in the study (45), or the relatively small number of participants enrolled in this study compared to studies for acetylcholinesterase inhibitors as memantine. The Cochrane collaboration meta-analysis showed a 3.78 improvement in the odds ratio of the Global Rating of Improvement (46).

With the advent of new drugs for AD dementia, many clinicians have not had significant improvements in demented patients as clinical trials have shown. Possibly, DEM should be revisited and attempted in AD dementia patients. DEM
may show even more promising effects on cognitive deficits, and more importantly, functional status as the above small studies have demonstrated. Nevertheless, it is important to remember that the complete pathophysiology of AD dementia has not been revealed; once this is understood, we can then develop that magic bullet to significantly impact the disease process and our aging patients.

Other nootropics have similarly been shown to be effective. Thus, piracetam had a 3.55 odds ratio of global improvement (47). Nicergoline, another ergot alkaloid, showed an improvement of 5.18 points on the Sandoz Clinical Assessment Geriatric scale, 2.86 points on the MMSE, and a global clinical improvement odds ratio of 3.33 (48). These studies have been criticized, as modern diagnostic techniques and rating systems were not always used; however, if anything, one would suspect that this would have made it harder to demonstrate a positive effect.

Vinpocetine, an ethyl ester of apovincamin (a vinca alkaloid from the lesser periwinkle), also increases cerebral blood flow. It produced no adverse effects in three trials of 583 participants, with a Cognitive Global Improvement of 5.27 (49).

Gingko biloba, according to the Cochrane meta-analyses, has produced Cognitive Global Improvement odds ratios from 2.16 (24 weeks) to 15.32 (12 weeks) (50). A recent article in the Journals has further supported this finding (51). Acetyl-L-carnitine’s odds ratio was 3.91 at 2 weeks and 2.33 at 12 weeks, but was not shown to directly improve cognition (52).

Free radical quenchers such as vitamin E have a potentially small effect on global improvement, but only one trial of good methodology exists (53). While animal studies for the free radical inhibitor, alpha-lipoic acid, appear promising (30,54), insufficient human data are available to support its evidence-based use at present (55).

This editorial has highlighted the fact that, while the drugs that are presently predominantly used for the treatment of AD are effective, other older and less expensive drugs appear to be equally effective. As these drugs act through different mechanisms, their combination with the newer drugs may be particularly advantageous. While these drugs may have little benefit to be studied by the mainstream pharmaceutical industry, we would strongly encourage the National Institute on Aging and the Alzheimer’s Disease and Related Disorders Association to pursue studies on these drugs. They should be included in approaches to the management of AD as clinically proven to be most likely effective.

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