Cognitive Interventions and Aging

Should One Use Medications in Combination With Cognitive Training? If So, Which Ones?

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In this article, we review current research regarding diagnosis of cognitive impairment in nondemented adults and discuss why medications and cognitive training together may be more beneficial than either alone. We also review potential cognitive enhancers and future research challenges. There are major reasons for such research: (a) Large numbers of older adults without dementia but with cognitive problems are not treatable with current cognitive training techniques; (b) some medications offer a rationale (i.e., cognitive enhancement) and some evidence that they might be a useful adjunct; and (c) there are unanswered questions about which population to target, which medications to use, how to administer them, and issues regarding tolerance and use of appropriate (active) placebo controls. As the number of cognitively impaired older adults grows, it is likely that there will be pressure to treat more broadly with both medications and cognitive training.

For a number of years, we have explored the ability of cognitive training to improve memory performance in nondemented older adults (Brooks, Friedman, Gibson, & Yesavage, 1993; Brooks, Friedman, Pearlman, Gray, & Yesavage, 1999; Brooks, Friedman, & Yesavage, 1993, 2003; Yesavage, 1985, 1989; Yesavage, Sheikh, Friedman, & Tanke, 1990; Yesavage & Rose, 1984a, 1984b). This work has involved training nondemented older adults with memory complaints in the use of mnemonic techniques, such as associative devices to link a person’s name with a prominent feature of his or her face or the “method of loci” to associate lists of objects with the visualization of a series of physical locations. As reported in this issue, these and similar efforts by other researchers generally have met with success. However, there remains a significant proportion of nondemented older adults who do not improve with such training (Hill, Yesavage, Sheikh, & Friedman, 1989; Kramer & Willis, 2002). It may be that the memory impairment of some of these nonresponsive individuals actually meets the criteria for mild cognitive impairment (MCI). MCI is a diagnosis that indicates a transitional stage between normal aging and dementia (Morris et al., 2001; Petersen et al., 1999). This article has several purposes: (a) to discuss some of the diagnostic issues relating to the screening of individuals for cognitive impairment and recruitment for programs of cognitive training; (b) to review the rationale and practical options for the use of dementia medications to enhance the response of such individuals to training; and (c) to discuss the benefits of other potential cognitive enhancing agents not currently indicated for the treatment of dementia, such as modafinil.

Diagnostic Issues

There have been several proposals regarding how best to characterize the spectrum of cognitive function in non demented older adults. MCI, age-associated memory impairment (AAMI), and age-related cognitive decline (ARCD) are among the proposed characterizations of cognitive function (Ferris & Kluger, 1996). The MCI diagnosis basically requires a documented memory deficit in the absence of other cognitive deficits consistent with dementia. Previous work by our group has projected that the conversion rate of nonaffected older adults to MCI may be as high as 11% by age 85 (Yesavage, O’Hara, et al., 2002). Individuals with MCI may convert to a diagnosis of AD at a rate of from 1% to as high as 25% per year (Petersen et al., 1999).

AAMI is a concept developed by a National Institute of Mental Health workgroup (Crook et al., 1986; Ferris & Kluger, 1996) to define the memory loss associated with normal aging. The criterion developed by this group for diagnosing AAMI was scores at least 1 standard deviation below the mean established for young adults on a normed, standardized test of recent memory. During the 1990s, there were extensive discussions between the National Institute of Mental Health AAMI Workgroup and the American Psychiatric Association regarding the possible inclusion of AAMI in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM–IV; American Psychiatric Association, 1994). After much debate, ARCD became the DSM–IV variant of AAMI. The Workgroup designed ARCD to encompass both memory and other cognitive changes associated with aging. To ensure that the ARCD label did not imply pathology, the American Psychiatric Association omitted the word deficit from its definition and placed ARCD in the “Other Conditions” section in the appendices of the DSM–IV. Major issues left unresolved in the DSM–IV were the specific diagnostic criteria required for the application of the diagnosis ARCD and discussion of how age and education could affect criteria.

Cognitive intervention trials in older adults typically select ARCD rather than MCI individuals for study. This is likely
because of their relative freedom from obvious neurological disorders despite their well-documented differences in memory performance compared to other age groups. For example, the primary screening instrument for a major National Institute on Aging MCI clinical trial is the Wechsler Memory Scale–Revised, Logical Memory II subtest (Petersen, Thomas, & Grundman, 2005). When one subtracts the expected score (50th percentile) for individuals aged 65–69 from that for individuals aged 20–24, the expected memory score declines by 27% with age (Wechsler, 1987). Although this decline alone is not severe enough to be considered either dementia or MCI, it remains a meaningful indication of substantial differences in memory performance between younger and older individuals. Given the cognitive demands of remaining functional in modern society, if such differences could be remediated, it is likely that older adults could remain more productive and active longer.

Even though more severe memory losses are associated with the diagnosis of MCI rather than with ARCD, these losses are not severe enough to be considered dementia without the finding of a second neurological deficit. Relevant criteria for dementia and for MCI are described in the DSM–IV criteria for dementia (American Psychiatric Association, 1994), National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria for AD (McKhann et al., 1984), and Petersen and colleagues’ (1995, 1999) criteria for MCI, further augmented (Petersen, 2004) for amnestic MCI or nonamnestic MCI, with impairment in a single or multiple domain(s). The cutoff criteria for memory dysfunction for MCI used in the recent National Institute on Aging trial of donepezil for MCI (Petersen et al., 2005) were memory function documented by scoring below the education-adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale–Revised (maximum score = 25 for Part A): less than or equal to 8 for 16 or more years of education, less than or equal to 4 for 8–15 years of education, and less than or equal to 2 for 0–7 years of education.” Thus, investigators set the criteria to be below a certain level of memory function without a floor (i.e., one can be essentially amnestic, carry the diagnosis of MCI, and not actually be diagnosed with dementia unless there is an impairment in a second cognitive domain—excluding memory—and these impairments lead to significant functional impairment).

To date, only one study has examined the effects of cognitive training in participants who met MCI diagnostic criteria; that study found no effects of training on cognitive variables (Rapp, Brenes, & Marsh, 2002). There were, however, no significant differences between groups on memory performance at posttest, although trained individuals showed a trend toward better word list recall than did controls. Rapp and colleagues did find that the treated group had significantly better memory self-appraisals than controls at the end of treatment and at a 6-month follow-up. This preliminary study did not consider the issue of medication use to augment the small responses to training seen in the MCI patients.

Finally, we should note that patients do not progress overnight from ARCD to MCI and then to AD. In earlier work, we modeled the prevalence of each cognitive state—not affected, MCI, and AD (Yesavage, O’Hara, et al., 2002). It is particularly interesting that the estimates suggested a prevalence of MCI of about 42% in 85-year-olds (i.e., greater than the prevalence of AD, which is 25% in this age group). Neuropathological data suggest that many cases of MCI actually represent early forms of AD (Morris et al., 2001). Whether or not an individual with MCI converts to AD, MCI in and of itself can be a cause of functional disability and is an important target for clinical interventions. Clearly, it would be a massive public health effort to improve function in MCI itself, let alone to target MCI patients for interventions to prevent AD.

**Rationale for the Use of Medications to Augment Cognitive Training**

**History of Combining of Medications and Other Therapies**

Psychiatric approaches to mental illness generally use a combination of medication plus psychotherapy. Even when the most commonly used approach is primarily medical (e.g., in schizophrenia), contact between the patient and the therapist is essential for maintaining the patient in treatment. In psychiatry, probably the best model for a combined treatment is the combination of antidepressant medication and cognitive behavioral therapy for depression. The limited efficacy of available drug compounds and the lack of standards for cognitive training complicate the development of analogous models that combine cognitively active medications and cognitive training (a skills training technique). The heterogeneity of the patient population, the neurodegenerative nature of the disorder, and the complexity of a theoretical rationale for any specific drug and training combination are other challenges facing the researcher in designing these studies.

**Theoretical Rationale for the Adjunctive Use of Medications: To Enhance Attention and Retention**

The rationale for the use of medication to improve the outcome of cognitive training is based on the following: To improve performance through the use of cognitive training, the individual must not only learn but also retain the training. Administration of a “memory pill” that works on improving encoding and subsequent recall of new information (in this case a mnemonic or associative memory aide) appears to be a straightforward solution. A researcher could expect that the patient who could not make use of the memory aide before receiving a pharmacologic intervention would be able to do so after the intervention. This would be analogous to priming the pump; in this case, giving the “memory pump” a boost to get it running. Patients then would be able to assimilate memory aids previously documented to be effective in normal older adults. By helping more impaired adults to benefit from training, this strategy might increase the overall number of patients who could benefit from psychological interventions.

However, attentional processes are involved in both encoding and recall of information; thus the concept of a pure “memory pill” is complicated by the fact that a “pill” that improved memory might do so by its effects on attentional processes rather than on memory per se. Thus, making rational choices about pharmacological interventions must include a close analysis of their specific pharmacologic effects as well
As a careful assessment of the patient’s cognitive deficits. The patient’s memory problem could be due to a loss of inherent capacity to encode and retrieve information or distractibility or preoccupation during either encoding or retrieval—or it may result from both disturbances. Clearly, it would do little good to add a medication enhancing memory function to a person whose inherent memory function was intact but who suffered from distractibility. Conversely, it would do little good to give a medication that might be expected to enhance sustained attention to a person who was already well focused but who was suffering from impairment of basic encoding and retrieval processes.

The classification of medications and interpretation of their effects is complicated by the relative sensitivity of cognitive tests to specific drug effects. Suppose, for example, that a medication actually had twice the effect on the cognitive processes involved in recall than it had on attentional processes, but the tests used to quantify attentional effects were three times more sensitive to drug effects than were the tests of recall used in the same experiment. Under these conditions, an experiment might show a preponderance of effects on attentional processes rather than recall, when in fact the inverse was true. Despite issues of test sensitivity, researchers have characterized most medications with cognitive effects by their effects on memory and learning processes as well as attentional processes.

**Candidate Medications: Donepezil, Memantine, Nicotine, and Other Stimulants**

Researchers have proposed a wide array of medications for the treatment of cognitive deficits, including MCI (Sherwin, 2000). These include a number of medications that affect neurotransmitters thought to change with aging and the development of dementia (acetylcholinesterase inhibitors or AChEIs), antioxidants, antiinflammatory medications, hormone replacement therapies, and medications that affect other processes involved in neuronal degeneration. Research has shown that some of these agents prevent or slow cognitive decline, whereas others, such as estrogen in women, have not been shown to be effective treatments for AD. The literature suggests that AChEIs may benefit processes that make it easier for older adults to assimilate and use mnemonics. Anticholinergics currently available in the United States include tacrine, donepezil, galantamine, and rivastigmine. These last two medications listed here have additional modes of action: Galantamine is an allosterically potentiating ligand of nicotinic acetylcholine receptors, and rivastigmine also inhibits butyrylcholinesterase. Scientists do not know if one of these AChEIs is more efficacious than the others in the treatment of AD. Recent studies and reports have raised concerns about the use of some antioxidants as well as antiinflammatories. This review focuses on medications already available in the United States for which there is both a rationale for use to enhance cognitive performance in older adults without dementias and some relevant experimental data.

**AChEIs, Donepezil**

Central cholinergic system deficiency is a hallmark of AD (Everitt & Robbins, 1997; Perry et al., 1978). Research has shown that AD patients have substantial neocortical deficits in choline acetyltransferase (Bowen, Smith, White, & Davison, 1976; Davies & Maloney, 1976; Perry, Gibson, Blessed, Perry, & Tomlinson, 1977), reduced choline uptake and acetylcholine release (Nilsson, Nordberg, Hardy, Wester, & Winblad, 1986; Ryllt, Ball, & Colhoun, 1983), and degeneration of cholinergic neurons of the nucleus basalis magnocellularis (Whitehouse, Price, Struble, Clark, & Coyle, 1982). Additional studies have demonstrated a significant reduction in the number of muscarinic and nicotinic acetylcholine receptors in AD brains (Francis, Palmer, Snape, & Wilcock, 1999; Little, Johnson, Minichiello, Weingartner, & Sunderland, 1998).

In addition to their associations with cortical pathology, cholinergic deficits are correlated with the degree of cognitive impairment in AD patients (Francis et al., 1999; Perry et al., 1978). This has led to the cholinergic hypothesis of Alzheimer’s disease (Bartus, Dean, Beer, & Lippa, 1982; Francis et al., 1999). AChEIs inhibit the enzyme acetylcholinesterase, which metabolizes acetylcholine. Thus, by increasing the concentration and duration of action of acetylcholine in synapses, AChEIs may be more physiologically beneficial than direct cholinoreceptor activation. Acetylcholinesterase inhibition leads to an indirect activation of muscarinic and nicotinic receptors. Because both of these receptors are reduced in AD patients, AChEIs might lead to more favorable results than single direct stimulation of either receptor alone.

Researchers have reported an age-related decrease in the presynaptic activity of choline acetyltransferase in humans (McGeer & McGeer, 1976). Choline acetyltransferase is considered to be a marker of cholinergic neurons; thus, its decline with age indicates a loss of cholinergic neurons with increasing age. Because postsynaptic muscarinic receptor binding also decreases with age (White et al., 1977), it appears that both presynaptic and postsynaptic cholinergic degeneration are involved in the process of normal aging. Research spanning more than 20 years has found that administering AChEIs to older adults produces improved performance on long-term and recent memory as well as working memory and recognition tasks (Davis et al., 1978; Furey et al., 1997).

The cholinergic hypothesis receives support from studies of nondemented adults that have reported that cholinesterase inhibitors improved cognitive performance (Davis et al., 1978; Muir, 1997). A cerebral blood flow study using healthy human volunteers (age range 22–68 years) found that administration of the cholinesterase inhibitor phystostigmine was associated with improved working memory efficiency, as indicated by faster reaction times and by reduced activation of cortical regions associated with working memory (Davis et al., 1978; Furey et al., 1997). Another investigation that used functional magnetic resonance imaging found that phystostigmine enhanced neural processing in visual cortical areas during a visual working memory task, particularly during encoding (Furey, Pietrini, & Haxby, 2000). Furey and colleagues suggested that augmenting cholinergic function may improve working memory by enhancing the selectivity of perceptual processing during encoding. The association of cholinergic drugs with better attention has led investigators to suggest that part of the benefit of cholinergic drugs upon memory performance may be mediated through enhancement of the attentional processes involved in working memory (Everitt & Robbins, 1997; Furey et al., 2000; Muir, 1997).
Saykin and colleagues (2004) performed the only study that related brain activity to donepezil’s cognitive effects in patients with MCI. This study explored the relation between performance on several working memory tasks in MCI patients who were given donepezil for approximately 6 weeks. Increased frontal activity was positively associated with improvement in working memory performance as well as baseline hippocampal volume. Saykin and colleagues suggested that donepezil-related improvement is mediated via alterations in the frontal lobes and hippocampus. There have been no systematic investigations on the effects of memantine, rivastigmine, or galantamine on cognition in healthy adults or patients with MCI (Ihl, 2003), nor have there been any studies of the effects of these drugs on memory training in humans.

The suggestion of a substantial attentional component to donepezil’s effects receives support from our own data from an experiment that used donepezil to enhance older aviators’ learning and performance of a complex aviation task (Yesavage, Mumenthaler, et al., 2002). These data showed that the strongest donepezil effects were on performance of emergency tasks and the approach to landing. The approach to landing requires sustained divided attention as well as a number of other cognitive functions (Taylor, O’Hara, Mumenthaler, & Yesavage, 2000). Although these findings appear to support interpretations of the effects of cholinergic augmentation on cognitive processing, particularly in relation to modulation of attentional processes, the precise neurochemical mechanisms of action remain to be fully delineated.

Requena and colleagues (2004) examined the effects of donepezil on performance in dementia patients who received a cognitive stimulation training. This study involved 86 patients with mild to moderate AD, all of whom received 10 mg of donepezil daily. A subgroup received cognitive training intended to stimulate awareness of orientation, body, social connection, self-care, reminiscence, household activities, animals, people, and objects. The results over a 1-year follow-up suggested that participants who received the combined treatment had a better response than those who did not receive any cognitive training. Although this study is intriguing, participants who did not receive training did not receive an active control. An October 2005 Medline search revealed that no other combined medication and cognitive training studies have been published, except for one that used piracetam, a medication not available in the United States. In that study, Israel, Melac, Milinkewitch, and Dubos (1994) treated 135 older adults with AAMI. They used a double-blind randomized trial methodology with cognitive training and with one of three drug interventions: placebo, 2.4 g of piracetam, or 4.8 g of piracetam (a nootropic drug of unknown mechanism, thought to enhance mental performance). The combination of piracetam and memory training resulted in significantly better performance on measures of immediate and global recall than researchers observed with memory training combined with placebo. The combined pharmacological and training approach appeared to be most effective in patients whose baseline performance on memory tests was lowest.

Memantine

The U.S. Food and Drug Administration approved memantine (Namenda) in October 2003 for treatment of moderate to severe AD. Memantine is classified as a noncompetitive low-to-moderate affinity N-methyl-D-aspartate (NMDA) receptor antagonist, which allegedly works by regulating the activity of glutamate. Some experts argue that glutamate plays a role in learning and memory by triggering NMDA receptors to allow a controlled amount of calcium to flow into a nerve cell. Excess glutamate, however, overstimulates NMDA receptors to allow too much calcium into nerve cells, leading to disruption and cell death. Some have argued that memantine may protect cells against excess glutamate by partially blocking NMDA receptors. Animal studies are the primary basis for this rationale for use (Miguel-Hidalgo, Alvarez, Cacabelos, & Quack, 2002; Rogawski & Wenk, 2003).

Several clinical trials indicate that memantine is efficacious in the treatment of cognitive and clinical symptoms associated with moderate to severe AD (Areosa & Sherriff, 2003). A double-blind placebo controlled 28-week study of 252 patients with moderate to severe AD showed a small but statistically significant benefit for those taking memantine on a test of their ability to perform daily activities and on the Severe Impairment Battery, a test designed to measure cognition in profoundly incapacitated individuals. Memantine recipients also showed a benefit on the Clinician Interview-Based Impression of Change Plus, a measure of overall function (Reisberg et al., 2003).

In a separate study, investigators randomly assigned 404 patients with moderate to severe AD (initial Mini-Mental State Examination scores ranging from 5–14), who had been taking donepezil for at least 6 months, to receive either 10 mg of memantine or a placebo twice a day in addition to donepezil. Those receiving memantine showed a statistically significant benefit in performing daily activities and on the Severe Impairment Battery, whereas participants taking donepezil plus placebo continued to decline (Tariot et al., 2004). Although one trial of memantine in mild to moderate AD reported some clinical benefits (Peskind et al., 2004), two other unpublished studies did not. Therefore, the efficacy of memantine in mild AD remains unclear.

Nicotine and Other Stimulants, Including Modafinil

Although few medications, including AChEIs, seem to have direct effects on memory per se, there are other medications that are likely to affect attentional mechanisms. For many years researchers have argued that optimal cognitive functioning depends upon achieving an optimal level of arousal (Yerkes & Dodson, 1908). Clearly many medications, such as amphetamines and other stimulants or sleeping pills and other sedatives, can moderate level of arousal (Yesavage, 1990).

Studies of aged animals have found nicotinic receptor agonists to be associated with improvements in learning and delayed recall performance (Arendash, Sengstock, Sanberg, & Kem, 1995; Prendergast et al., 1997). Research has shown that nicotine improves aspects of cognitive performance, such as attentional function, in humans with early-stage AD (Everitt & Robbins, 1997; Sahakian, Jones, Levy, Gray, & Warburton, 1989) as well as in healthy persons.

We also tested nicotine in our aviation model described previously (Mumenthaler, Taylor, O’Hara, & Yesavage, 1998). We found that both donepezil and nicotine affected flight simulation tasks that required sustained attention (Mumenthaler...
et al., 2003). A practical difficulty is that many of the medications that could enhance arousal (for example, amphetamines or nicotine) have characteristics, such as potential for abuse and development of physiological addiction and tolerance, that limit their usefulness. Moreover, more recently others have reported that current smoking may predict a poor response to AChEIs (Connelly & Prentice, 2005). Thus the possible role of transdermal nicotine remains unclear.

An extensive literature exists regarding the use of the stimulant amphetamine in military aircraft pilots as a countermeasure for high-fatigue situations. Aviation researchers have now begun the systematic study of modafinil (Provigil), an approved treatment for narcolepsy, in these high-fatigue aviation situations. Modafinil has been used by the U.S. Air Force as an alternative to amphetamine (the so-called Go Pill) to keep pilots awake. Flight simulation studies suggest that modafinil is probably less effective than amphetamine but better than placebo (Caldwell, Caldwell, Smith, & Brown, 2004). Three double-blind placebo controlled studies of non-sleep-deprived pilots (Turner et al., 2004). A practical difficulty is that many of the medications designed to enhance the ability to hold information in working memory, attention, or executive functioning (Sevy et al., 2005; Spence, Green, Wilkinson, & Hunter, 2005) that had been suggested by earlier pilot studies (Rosenthal & Bryant, 2004; Turner et al., 2004).

Modafinil is well tolerated and may be used in low doses during flight operations. This suggests that it may also be tolerated in populations such as elderly adults, where its effects on cognition may be studied.

**Approach to Future Studies**

**Which Drugs to Study?**

We are currently studying the use of donepezil as an augmentation strategy to enhance the effects of cognitive training in normal older adults and in those diagnosed with MCI (National Institute of Mental Health Grant R01 MH35182). The study is a double-blind randomized clinical trial in which all participants receive the cognitive training performed in previous studies (e.g., Yesavage & Rose, 1984a, 1984b) with either 10mg of donepezil daily or placebo. Participants receive either drug or placebo for 12 weeks prior to receiving the cognitive training. They are followed for 9 months after the 2-week training. Preliminary results of this study may be available later in 2007.

The next most likely candidate for study may be memantine. Researchers should consider this medication because it, like donepezil, is approved for use in AD patients. However, randomized clinical trials with this medication have been less successful in more mildly impaired AD patients than in more severely impaired patients; this is in contrast to donepezil trials, in which scientists saw better results in mild to moderate patients. The memantine results in relation to the severity of AD may be due to milder populations having a larger placebo effect than those carried out in more severely impaired populations.

**Design Issues**

**Baseline characteristics.**—A major challenge in research on combined pharmacological and cognitive training protocols is determining which participant characteristics at baseline have the potential to moderate treatment effects. Our initial efforts in this area involved identifying the relations between baseline levels of cognitive deficits and the efficacy of the cognitive training. We found that even subtle impairments could have detectable effects on performance after training (Yesavage, Sheikh, Friedman, & Tanke, 1990). Many participant characteristics may affect performance. Personality (Gratzinger, Sheikh, & Yesavage, 1999), hearing impairment (Pearman, Friedman, Brooks, & Yesavage, 2000), chronological age (Yesavage et al., 1990), performance on a variety of cognitive tests (McKichrick et al., 1999), cultural considerations (Yesavage et al., 1999), estrogen replacement therapy (Robinson, Friedman, Marcus, Tinklenberg, & Yesavage, 1994), preexisting mnemonic strategies (Brooks, Friedman, Gibson, et al., 1993), attention (Yesavage, 1990), and apolipoprotein E status (O’Hara et al., 1998) are all factors that affect memory performance and, potentially, response to training.

McKichrick and colleagues (1999) identified participant characteristics associated with successful response to training. As did our earlier work with the Mini-Mental State Examination (Hill et al., 1989; Yesavage et al., 1990), McKichrick’s work suggested that results at baseline on specific tests such as Wechsler Paired Associates and the Symbol Digit Modalities Test were associated with successful response to training. Research reports that poor performance on the Object Rotation task (Schaeie, 1985) predicts a poor response to cognitive training overall (McKichrick et al., 1999). Scientists can incorporate findings such as these into studies designed to target specific abilities (in this case, object rotation). Thus, a cycle of assessment and modification of interventions can ultimately lead to improved interventions.

**Type of cognitive training.**—Training that focuses on improvement of episodic memory is the most obvious target of intervention, since currently available medications of demonstrated safety, such as donepezil, are thought to enhance that function. Other training targets, such as the ability to perform complex tasks described by Kramer and Willis (2002) or the ability to conduct efficient visual information processing described by Ball and associates (2006), might benefit from medications designed to enhance the ability to hold information in working memory. Many cognitive tasks require maintenance of information in working memory. Any medications that could improve this function might be worthy of exploration.

**Timing of drug treatment: Before or after training, or forever?**—Another issue is whether participants should use the medication prior to and concurrently with the training to augment the retention of training itself, or whether they should use the medication after training is completed as an independent
intervention designed to improve memory performance regardless of its effects on retention of training. These routes are not mutually exclusive; however, we emphasized the former route since we had evidence that participants were not assimilating the cognitive training techniques. Because it is possible that a medication with effects on memory could enhance learning of cognitive techniques as well as directly enhance performance on the target symptoms, research designs should try to tease apart the two effects. This is important because if the medication in question enhances retention of the technique, it might become a generalized tool that could enhance the retention of any cognitive technique regardless of whether the technique itself targeted memory. Furthermore, it may be important to discern if the medication treatment is only needed at the point of training and can be discontinued afterwards, or if it needs to be maintained permanently so that the technique learned while on medication may be retained (state-dependent learning). The issue of drug continuation after the training period may also be salient to a question that has long concerned those in the area of cognitive training: Will training in the lab transfer out of the lab into people’s everyday lives (Robertson-Tschabo, Hausmann, & Arenberg, 1976)?

Dosage, side effects, and blinding of investigators and patients.—A difficult issue in the use of cognitively enhancing medications is blinding of both researchers and patients from awareness of drug effects. Unless a good placebo is available, a placebo control may not be possible. There may be studies in which the active medication may have such significant side effects as to be easily discernable by patient and researcher alike. This becomes an issue in medication selection, as it favors the choice of a medication with the fewest side effects (e.g., donepezil as opposed to tacrine).

Tolerance and withdrawal.—Finally, if investigators were to find a medication that has positive effects on cognition in the ARCD population with or without the use of cognitive training, safe withdrawal of the medication may become an issue. If, for example, a clinical trial of nicotine found that it enhanced cognitive performance, what would be the end result for the patient once the medication was withdrawn? One could raise this issue for many types of medication for which the risks of developing tolerance to the medication as well as its safety during withdrawal are unknown.

Ethical Issues on Medication Use

Finally, despite the theoretical and practical reasons driving the search for medications that might have cognitive effects in nondemented populations to enhance the effects of cognitive training, some have raised ethical issues about the use of such compounds for this purpose (Whitehouse, Juengst, Mehman, & Murray, 1997). One of the key issues includes whether or not investigators should make attempts to ameliorate “normal” changes with aging. This question is usually answered with reference to effective treatment for visual and hearing losses with aging. More difficult questions arise in terms of how to defray the costs of any pharmacological treatment with the potential to ameliorate memory losses with aging. Given that pharmaceutical costs could run to more than $100 per month, how would such costs be paid? Who would pay for the less fortunate members of society? If society did not accept the burden, would it be morally just for those who could afford to pay for such treatments to receive them while others could not have them? In any case, posing these questions may be premature given the equivocal state of evidence for the effectiveness of medications for improving memory. At the very least, as investigators make progress in providing effective treatments for ARCD, it will become more likely that interventions will involve medications and thereby raise questions about the cost-effectiveness of the proposed treatments.

Conclusions: Should One Use Medications in Combination With Cognitive Training?

In summary, the spectrum of cognitive impairment in older adults ranges from normal aging through milder stages of cognitive impairment (from ARCD and MCI) to actual dementia. However, the exact models of transition remain uncertain at this time. The combination of medications for both cognitive enhancement and cognitive training may lead to increased improvements in attention and recall of information. Candidate medications that could be investigated include donepezil, memantine, nicotine, and modafinil. Targets for cognitive interventions include the improvement of episodic memory, the ability to perform complex tasks, and the ability to conduct efficient visual information processing.

In conclusion, there are several important reasons to support research on the use of pharmacological augmentation of cognitive training. First, there are large numbers of older adults with cognitive problems who do not meet criteria for AD but for whom cognitive training as currently practiced may not be effective. Second, some medications offer at least some rationale and preliminary evidence that they might be useful to test in treatment-resistant older adults. However, there are many unanswered questions about the best methods by which to target a susceptible population, which medications to use, how to administer them, and how to handle technical issues regarding tolerance and development of proper (active) placebo controls. Nonetheless, as the population of cognitively impaired older adults grows, it is likely that so will the need to treat more broadly with medications, cognitive training, and both interventions together.

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