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Delirium in Early-Stage Alzheimer's Disease:

Enhancing Cognitive Reserve as a Possible Preventive Measure

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Abstract

Delirium is a disorder of acute onset with fluctuating symptoms and is characterized by inattention, disorganized thinking, and altered levels of consciousness. The risk for delirium is greatest in individuals with dementia, and the incidence of both is increasing worldwide because of the aging of our population. Although several clinical trials have tested interventions for delirium prevention in individuals without dementia, little is known about the mechanisms for the prevention of delirium in early-stage Alzheimer's disease (AD). The purpose of this article is to explore ways of preventing delirium and slowing the rate of cognitive decline in early-stage AD by enhancing cognitive reserve. An agenda for future research on interventions to prevent delirium in individuals with early-stage AD is also presented.

Delirium is a disorder of acute onset with fluctuating symptoms and is characterized by inattention, disorganized thinking, and altered levels of consciousness. The risk for delirium is greatest in individuals with dementia, and the incidence of both is increasing worldwide because of the aging of our population. Although several clinical trials have tested interventions for delirium prevention in individuals without dementia (Inouye, 2006), little is known about the mechanisms and models for the prevention of delirium in early-stage Alzheimer's disease (AD). We do know that delirium occurs frequently in individuals with dementia and that outcomes for patients with delirium and dementia are poor (Fick, Agostini, & Inouye, 2002). As increasing numbers of people are diagnosed at earlier stages with AD and related dementias, attention to preventable and treatable problems like delirium are crucial to the care of individuals with AD.

The purpose of this article is to explore ways of preventing delirium and slowing the rate of cognitive decline in early-stage AD by enhancing cognitive reserve, a promising new area of research. We begin by defining delirium in dementia, its prevalence, and outcomes in early-stage AD. We then define cognitive reserve and review the literature that supports its association to dementia and delirium. Finally, we set an agenda for future research on interventions to prevent delirium in individuals with early-stage AD.

DEFINITIONS AND OUTCOMES FOR DELIRIUM IN EARLY-STAGE AD

According to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (American Psychiatric Association [APA], 2000), and as noted above, delirium due to a general medical condition includes an alteration of consciousness, change in cognition, acute onset, fluctuating course, and reduced attention. For the purposes of this review, early-stage AD is defined as having a diagnosis of early-stage AD or dementia with a Mini-Mental State Examination score greater than 17, Clinical Dementia Rating Scale scores of 0.5 to 2.0, or a Global Deterioration Scale score of 2.0 or less (Burgener et al., 2008).

Delirium is superimposed on dementia when an acute change in mental status (characterized by a fluctuating course, inattention, and either disorganized thinking or an altered level of consciousness) occurs in a patient with preexisting dementia (APA, 2000). The pathogenesis of delirium is poorly understood but is known to share several overlapping features with dementia (Inouye, 2006). Although delirium and dementia are often separated clinically and methodologically, they often occur together and are probably highly interconnected. Recent literature suggests that delirium and dementia may represent points along a continuum, with delirium reflecting underlying brain vulnerability in early-stage dementia (Hsieh, Fong, Marcantonio, & Inouye, 2008). Thus, interventions that are protective for dementia may also help prevent delirium or reduce its severity.

Although the presence of dementia has been shown to be an independent risk factor for delirium (Inouye, 2006), many studies exclude individuals with dementia. Several studies have reported higher rates of hospitalization in individuals with dementia compared with those without dementia, which may put them at risk for developing delirium (Chodosh et al., 2004; Fick, Kolanowski, Waller, & Inouye, 2005). Delirium often occurs in the hospital setting but may occur even more frequently in community-dwelling individuals with dementia. The prevalence of delirium superimposed on dementia (DSD) ranges from 22% to 89% in both hospital and community settings (Fick et al., 2002).

The onset of delirium is associated with poor outcomes, including functional decline, increased hospitalizations, increased health care use, nursing home placement, and death (Baker, Wiley, Kokmen, Chandra, & Schoenberg, 1999; Fick & Foreman, 2000; Fick et al., 2005; McCusker et al., 2001; O'Keeffe & Lavan, 1999). A study by Fick et al. (2005) found patients with DSD had the highest health care costs and use compared with patients with delirium alone, dementia alone, and those with neither dementia nor delirium. Bellelli, Speciale, Barisione, and Trabucchi (2007) analyzed four matched samples of older adults consecutively admitted to a rehabilitation unit and found that patients with DSD had significantly higher mortality than patients with delirium or dementia alone. Prevention and improved management of delirium in dementia is clinically important and urgently needed.

COGNITIVE RESERVE AS A MECHANISM FOR DELIRIUM IN DEMENTIA

Work by Katzman et al. (1988) was one of the earliest references to the idea of *reserve* as it relates to clinical manifestations of brain disease. The concept of reserve helps explain the lack of association often seen between actual disease pathology and clinical manifestations of the disease. In their seminal study, a number of individuals who exhibited little evidence of AD in life were found to have extensive pathology on postmortem examination. The researchers concluded that these individuals may have started with more neurons (i.e., reserve) than those individuals who had similar pathology but who did exhibit clinical signs and symptoms.

As a theoretical framework for understanding the manifestation of brain pathology, reserve has come to include both passive and active processes in the brain that modify risk for the clinical expression of brain disease. Passive reserve is often referred to as *brain reserve* and

posits that there are individual differences in the amount of brain damage one can endure before exhibiting clinical signs and symptoms. These threshold differences are accounted for by brain size and synapse density (Stern, 2002).

Active reserve is often referred to as *cognitive reserve* and posits that individuals differ in the degree of efficiency with which they can use brain networks or cognitive strategies to cope with brain pathology. These differences are hypothesized to be due to mental stimulation that individuals are exposed to over a lifetime, including level of educational attainment, occupational complexity, and the mental complexity of leisure activities (Valenzuela & Sachdev, 2006).

Brain reserve and cognitive reserve are not mutually exclusive; animal studies have demonstrated that mental stimulation in the form of environmental enrichment is a strong signal for the generation of neurons and synapses (van Praag, Kempermann, & Gage, 2000). Neurons and synapses are the substrate on which brain networks are built and enhanced synaptic activity (more efficient brain networks) might exist in individuals who engage in mentally stimulating activities (Scarmeas & Stern, 2003). In this regard, reserve is not a static central nervous system (CNS) property, and evidence for the capacity to develop compensatory mechanisms in late life and early-stage AD is now emerging.

We use the term *cognitive reserve* in this article to refer to mechanisms that may prevent delirium in dementia because it is behaviorally defined and therefore carries greater clinical relevance than the term *brain reserve*. The literature that supports the idea of cognitive reserve and prevention of brain pathology is reviewed below.

INTERVENTIONS SHOWING PROMISE FOR INCREASING COGNITIVE RESERVE

Most of the research has demonstrated an association between cognitive reserve and risk for AD (Valenzuela & Sachdev, 2006), and although it has not yet been fully tested in delirium trials, one possible mechanism for delirium prevention in early-stage AD is the enhancement of cognitive reserve in individuals with dementia. The existing evidence on prevention of cognitive decline and enhancement of cognitive reserve is important for understanding the prevention of delirium in early-stage AD. Those interventions that have the strongest links to improving cognitive reserve in individuals with brain pathology, particularly dementia, include physical activity, social interaction, challenging mental activities, and avoidance of anticholinergic drugs and inappropriate medications (Table 1).

Physical Activity

Physical activity studies have demonstrated strong associations between exercise and dementia risk (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), but the extent to which cognitive research from exercise may be protective against delirium is currently speculative. Laurin et al.'s (2001) longitudinal Canadian study of 4,615 community-dwelling men and women age 65 and older who were dementia free at baseline investigated associations between regular physical activity and risk of cognitive decline. At 5-year follow up, participants who performed some level of exercise had less risk of cognitive impairment, AD, and dementia of any kind compared with participants with no regular exercise (Laurin et al., 2001). Outcomes of Podewils et al.'s (2005) U.S. study of 3,375 men and women age 65 and older who were dementia free at baseline supports the theory that noncarriers of APOE*E4 who participate in a number of different physical activities have protection against dementia risk.

Several other studies have demonstrated that participants undertaking regular physical activity (2 to 3 times per week, 15+ minutes per session) are less likely to have dementia than control

groups with less or no exercise (Rovio et al., 2005; van Gelder et al., 2004). Stemming from these findings, it has been claimed that physical exercise stimulates trophic factors and neural growth, a potential mechanism resulting in provision of cognitive reserve in later life (Dik, Deeg, Visser, & Jonker, 2003). A recent study found self-report of participation in regular exercise to be protective against delirium (Yang et al., 2008). Although there are limited studies in this area, recommended interventions for delirium prevention include mobility and walking.

Social Activities and Support

Longitudinal studies have shown that social networks and social engagement have a protective influence on cognitive function, especially in women (Crooks, Lubben, Petitti, Little, & Chiu, 2008; Zunzunegui, Alvarado, Ser, & Otero, 2003). Socially engaging activities involving children, family, and friends, especially at midlife, have been associated with a decreased risk of dementia (Lindstrom et al., 2005; Wilson et al., 2002; Zunzunegui et al., 2003). Frequent interactions with large social networks, leisure pursuits, being married, and perceived positive support from friends are also positively correlated with maintenance of cognitive function (Elwood et al., 1999; Holtzman et al., 2004; Yeh & Liu, 2003).

Challenging Mental Activities and Cognitive Stimulation

Brain plasticity is the term used to describe the brain's ability to compensate the effects of insults through structural and functional changes (Pascual-Castroviejo, 1996). On the basis of animal studies and clinical trials in human beings, plasticity theory suggests that rehabilitative interventions may facilitate neuronal reorganization and recovery of function, supporting the idea that cognitive recreational activities may be protective (Albensi & Janigro, 2003).

Evidence supports the concept that mental stimulation may increase cognitive reserve and decrease the rate of age-related cognitive decline (Le Carret et al., 2005; Newson & Kemps, 2006). Various studies have found significant relationships between stimulation of the brain and decrease in cognitive decline, with some finding that higher education in earlier life may reduce, delay, or protect against cognitive decline in later years (Gatz et al., 2001; Lyketsos, Chen, & Anthony, 1999; Schmand, Smit, Geerlings, & Lindeboom, 1997).

Having more years of education has been shown to have a protective effect on cognitive decline, and people with higher levels of education have greater brain reserves (Gatz, 2005; Gatz et al., 2001). A study of 326 Canadian World War II veterans showed that young adult intelligence was the most important determinant of older adult performance (Gold et al., 1995). Supporting this are the findings that occupations that are intellectually more difficult and challenging (Schmand et al., 1997) and increased years of formal education (Lyketsos et al., 1999) can have a protective effect on cognitive decline. Education occurring at any age can be protective, and that protection occurs through adulthood, not just in old age (Farmer, Kittner, Rae, Barko, & Regier, 1995; Lyketsos et al., 1999).

Pursuing this further, the question of whether decline can be altered in cognition has been answered to some degree in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Study. This randomized, controlled, single-blind study ($N = 2,832$, age range = 65 to 94) investigated the effect of cognitive training on mental ability (Ball et al., 2002) with a 5-year follow up (Willis et al., 2006). Findings from this study suggest that cognitive training can improve cognitive functioning, and improvements can be sustained over 5 years. Supporting this was a small case-control study ($N = 24$, 12 cases and 12 controls) that evaluated the benefit of cognitive stimulation in elderly people with mild cognitive impairment compared with cognitively intact participants (Wenisch et al., 2007). This study used reality orientation techniques, mental imaging, recall and delayed recall, and executive exercises as cognitive stimulating exercises. Findings suggested that cognitive stimulation can improve memory in older adults with mild cognitive impairment (Wenisch et al., 2007). Several home-

based cognitive stimulating studies have shown that reading of newspapers, pursuit of hobbies, and participation in leisure activities are all capable of improving cognition and increasing cognitive reserve in older adults (Mackinnon, Christensen, Hofer, Korten, & Jorm, 2003; Newson & Kemps, 2006).

Anticholinergic and CNS-Active Medication Use

Studies have shown that categories of prescription drugs with anticholinergic and CNS-active properties are associated with low cognitive performance in older adults (Lechevallier-Michel, Molimard, Dartigues, Fabrigoule, & Fourrier-Raglat, 2005; Mintzer & Griffiths, 2007). These encompass drugs commonly taken by older adults, including some kinds of antihistamine drugs, bronchodilator medications, some antipsychotic agents, antinausea medicines, anti-anxiety agents, antidepressant drugs, cardiovascular agents, and Parkinson's disease medications (Lechevallier-Michel et al., 2005; Napoli, 2008). Although not independent predictors of the development of dementia, people who had taken these kinds of medications consistently were more likely to have a diagnosis of mild cognitive impairment at 1-year follow up (80%) than nonusers (35%), and anticholinergic drug use was a strong predictor of mild cognitive impairment (odds ratio = 5.12, $p = 0.001$) (Ancelin et al., 2006).

People who have taken these medications can have CNS side effects, such as memory and attention deficits and delirium, even when dosages are taken at recommended levels (Lechevallier-Michel et al., 2005; Moore & O'Keeffe, 1999). In a study using administrative data on 960 individuals with dementia, 79% were on CNS-active drugs. These CNS drugs were associated with an increased risk of falls, fractures, and delirium in individuals with dementia (Fick, Kolanowski, & Waller, 2007). Although studies have been conflicting as to whether individuals with dementia take more potentially inappropriate medications, these drugs have also been associated with delirium and cognitive decline in individuals with dementia (Fick & Mion, 2008; Kolanowski, Fick, Waller, & Ahern, 2006).

COGNITIVE RESERVE AND DELIRIUM SUPERIMPOSED ON DEMENTIA

In at least two studies, individuals with low levels of educational attainment were at greater risk for delirium than individuals with more education (Jones et al., 2006; Pompei et al., 1994). In a recent prospective study of 779 newly admitted elderly hospitalized patients without dementia, participation in regular exercise was found to be protective against delirium (Yang et al., 2008).

There is an expanding body of evidence examining delirium in individuals with dementia, but only a few controlled trials have reported data on interventions to prevent delirium in individuals with dementia, and none of these trials reported data for individuals with early-stage AD. Many intervention studies for delirium prevention in the past 10 years have not included individuals with dementia, did not measure or report dementia stage, or did not have sufficient power to analyze individuals with dementia separately (Britton & Russell, 2004; Fick et al., 2002; Lundström et al., 2005; Naughton et al., 2005). Strategies to prevent or decrease the severity of delirium usually focus on multicomponent interventions, including consultation by a geriatrician, early mobilization, hydration, decreasing psychotropic medication, cognitive stimulation, and nursing care interventions.

A controlled clinical trial by Inouye et al. (1999) that included individuals with dementia found that fewer patients in the treatment group (22 of 128 [17%]) developed DSD compared with the usual care group (40 of 125 [32%]). The most effective part of their intervention for individuals with dementia was the non-pharmacological sleep protocol. As increasing numbers of individuals are diagnosed with dementia at earlier stages, increased attention to

understanding the mechanisms involved in prevention of delirium will be crucial for this growing population.

The evidence indicates that mental and physical activity builds cognitive reserve, but there are also factors that may reduce cognitive reserve. The presence of dementia, depression, dehydration, immobility, sensory impairment, multiple comorbidities, and use of certain classes of drugs are risk factors for delirium. It is important to address these potential factors when designing a program of delirium prevention.

IMPLICATIONS FOR FUTURE NURSING RESEARCH

Despite poor outcomes associated with DSD, only a few studies have analyzed the prevention of delirium in individuals with dementia, the results of which have been mixed. No studies have addressed delirium in individuals with early-stage AD. The overall evidence for delirium prevention models in early-stage AD is weak due to a low number of randomized trials with inconsistent results, as well as the exclusion of individuals with dementia in most delirium trials (Atkins et al., 2004). However, the use of cognitive stimulation and recreational activities and the avoidance of CNS-active medications hold great promise to decrease delirium incidence and severity in early-stage AD. This approach requires more testing in rigorous trials.

Although most of the current work regarding the enhancement of cognitive reserve has been conducted in populations of individuals with dementia, there is emerging evidence that similar mechanisms may prevent delirium in this population (Jones et al., 2006; Mudge, Giebel, & Cutler, 2008; Pompei et al., 1994). Delirium is higher in individuals with dementia than any other subgroup of disease, and dynamic models specific to enhancing cognitive reserve and preventing delirium in early-stage AD are urgently needed. Table 2 outlines an agenda for future nursing research in this area.

CONCLUSION

There are tremendous public health implications for developing a delirium prevention program in early-stage AD, a time when there is still significant potential for rehabilitation (Yu, Evans, & Sullivan-Marx, 2005). Because delirium leads to many poor health outcomes (Bellelli, Frisoni, et al., 2007), prevention of delirium has the potential for significant personal, social, and economic benefits. Prospective studies that test current and future intervention models will aid the understanding of the needs of individuals with dementia across care settings and allow evidence-based guidelines to be developed and implemented for delirium prevention in early-stage AD.

KEYPOINTS

1. As growing numbers of older adults are diagnosed at earlier stages of Alzheimer's disease (AD) and related dementias, attention to preventable and treatable problems such as delirium are crucial to the care of individuals with dementia.
2. Delirium and dementia are increasingly known to be closely connected; thus, interventions that are protective for dementia may also help prevent delirium or reduce its severity.
3. One possible mechanism for delirium prevention in early-stage AD is the enhancement of cognitive reserve. Those interventions that have the strongest links to improving cognitive reserve in individuals with dementia include physical activity, social interaction, challenging mental activities, and avoidance of anticholinergic and inappropriate medication use.

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TABLE 1
INTERVENTIONS TO ENHANCE COGNITIVE RESERVE

Activity	Evidence	Web Resources
Physical and social activities <ul style="list-style-type: none"> Regular exercise at least twice per week for at least 15 minutes per session Reduced periods of inactivity (such as long periods of watching television), which increase cognitive decline Social networking with children, family, and friends Going to the movies, restaurants, clubs, centers, or sporting events Productive activity such as daily gardening, housework, cooking, and doing volunteer work 	Laurin et al. (2001); Lindstrom et al. (2005); Newson & Kemps (2006); Rovio et al. (2005); Simons et al. (2006); Verghese et al. (2003); Wang et al. (2002); Yang et al. (2008) (delirium specific)	AARP: 10 Steps to an Optimal Memory http://www.aarp.org/health/conditions/articles/harvard__improving-memory-understanding-age-related-memory-loss_6.html Alzheimer Society of Canada: Healthy Brain http://www.alzheimer.ca/english/brain/brain_intro.htm Alzheimer's Association: Brain Health http://www.alz.org/we_can_help_brain_health_maintain_your_brain.asp
Cognitive stimulation <ul style="list-style-type: none"> Leisure activities such as reading books and newspapers, writing for pleasure, doing crosswords and puzzles, playing card and board games, playing musical instruments Pursuing further education in early life to midlife 	Ball et al. (2002); Lyketsos et al. (1999); Verghese et al. (2003); Wilson et al. (2002)	About Memory: Mental Stimulation http://www.memory-key.com/Seniors/stimulation.htm American Geriatrics Society: Aging in the Know http://www.healthinaging.org/agingintheknow/default.asp Hospital Elder Life Program (HELP) http://elderlife.med.yale.edu/public/interventions.php?pageid=01.03.04 Keep Your Brain Alive http://www.neurobics.com/index.html Posit Science http://www.positscience.com
Avoiding anticholinergic and potentially inappropriate medication use <ul style="list-style-type: none"> Providing older adults with a list of medications to avoid because the risks outweigh the benefits, and 	Fick et al. (2003); Hsieh et al. (2008); Rudolph et al. (2008)	Duke University's Potentially Inappropriate Medications for the Elderly According to the Revised Beers Criteria http://www.dcri.duke.edu/ccge/curtis/beers.html IPRO's Decreasing Anticholinergic Drugs in the Elderly Project http://providers.ipro.org/index/pres-drug-plan-prescribers

Activity	Evidence	Web Resources
<div>safer alternatives exist</div> <ul style="list-style-type: none">• Providing prescribers and health professionals with tools to identify anticholinergic and inappropriate medication use to distribute with patient handouts		

TABLE 2

A NURSING RESEARCH AGENDA FOR INTERVENTIONS TO PREVENT DELIRIUM IN EARLY-STAGE ALZHEIMER'S DISEASE (AD)

<p>Diagnosis and evaluation of delirium in early-stage AD. Need to refine and test instruments for delirium in early-stage AD. Issues to consider:</p> <ul style="list-style-type: none"> • Assess overlapping symptoms in delirium and early-stage AD. • Determine factors in early nurse/provider recognition of delirium in AD.
<p>Identify etiology/risk factors unique to delirium in early-stage AD:</p> <ul style="list-style-type: none"> • Develop models for determining individuals with early-stage AD at highest risk. • Determine factors most amenable to interventions across settings.
<p>Prevention of delirium through enhancement of cognitive reserve. Challenges to address:</p> <ul style="list-style-type: none"> • Individualization of cognitive activities. • Measuring effect of education and other reserve protective effects on training. • Defining and measuring cognitive reserve as an active mechanism. • Determine components of intervention most effective. • Measurement of trajectory of cognitive decline over time with AD/delirium. • Assess delirium management strategies most effective in early-stage AD. • Evaluate home prevention of delirium.
<p>Intervention methodology and design issues to consider:</p> <ul style="list-style-type: none"> • Initiation and maintenance of treatment. • Short-term versus long-term effects. • Randomizing patients by clusters rather than as individuals using a cluster randomized controlled trial (RCT) design. • Dosage and duration of intervention/activities. • Use of functional magnetic resonance imaging and biomarkers in assessing outcomes.
<p>Ethical issues to address:</p> <ul style="list-style-type: none"> • Identify best methods for promoting autonomy and ensuring protection of research, both in informed consent and in the conduct of the study itself, for participants who are at risk of or are experiencing delirium. • Assess decisional capacity of individuals with delirium for both treatment and research consent. • Determine measures for obtaining the most appropriate surrogate informed consent, when necessary. • Assess participants' understanding of study risk. • Evaluate when and how to notify clinicians of delirium in RCTs. • Establish postdelirium recovery information and counseling.
<p>Translational considerations for delirium interventions in early-stage AD:</p> <ul style="list-style-type: none"> • Kind of discipline/provider needed to best deliver intervention. • Best ways to facilitate adoption of intervention. • Use of informatics to deliver or enhance components of intervention. • Costing out intervention savings. • Financing of intervention. • Delivery across care settings.

- Organizational and leadership characteristics influencing adoption of intervention.