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***Our Mission:*** Helping to prepare Iowa's health practitioners to care for our growing population of elders. *E-NEWS* is one of our methods of teaching through technology.

Each month, *E-NEWS* delivers abstracts from current multidisciplinary healthcare journal articles related to a specific geriatric topic. This month's *E-NEWS* focuses on MEDICATIONS AND THE AGING BRAIN: AN OVERVIEW OF COMMON ISSUES IN GERIATRIC PSYCHOPHARMACOLOGY.

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## MEDICATIONS AND THE AGING BRAIN: AN OVERVIEW OF COMMON ISSUES IN GERIATRIC PSYCHOPHARMACOLOGY

In this issue of the *E-NEWS*, you will find abstracts for:

- A study that explores the impact of chronic use of anticholinergic medications on older adults' cognitive functioning.
  - An article that reviews pharmacodynamics in older adults.
  - A study that measures the anticholinergic activity of medications commonly used by older adults.
  - A study that examines data related to change in pharmacokinetics and pharmacodynamics in older adults.
  - A White Paper that presents an update on the use of antipsychotic drugs in older adults with dementia.
  - A study that evaluates antipsychotic therapy and short-term serious events in older adults with dementia.
  - A study that assesses the effect of central nervous system medication use on decline in cognition in community-dwelling older adults.
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- Bottiggi KA, Salazar JC, Yu L, Caban-Holt AM, Ryan M, Mendiondo MS, Schmitt FA. Long-term cognitive impact of anticholinergic medications in older adults. *Am J Geriatr Psychiatry*. 2006 Nov;14(11):980-4.

OBJECTIVE: The objective of this study was to determine whether chronic use of medications with anticholinergic (AC) properties impact older adults' cognitive functioning. METHODS: Six years of cognitive test data from two groups of older adults (AC and control) were examined retrospectively (N = 592). RESULTS: Declines over time were found for the AC group on parts A and B of the Trail Making Test. CONCLUSION: Physicians prescribing ACs to older adult patients should be aware of their potential effects on psychomotor speed and executive functioning. These cognitive effects may lead to impairments in daily functioning resulting in the need to reevaluate patient medications.



- Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother*. 2007 Sep;5(3):263-303.

BACKGROUND: Older individuals experience physiologic changes in organ function related to aging or to specific disease processes. These changes can affect drug pharmacodynamics in older adults. OBJECTIVE: The goal of this article was to review age-related changes in pharmacodynamics and their clinical relevance. METHODS: PubMed and International Pharmaceutical Abstracts were searched (January 1980-June 2006) for the following combination of terms: pharmacodynamic and elderly, geriatric or aged. References cited in other reviews were also evaluated. The current review focused on age-related pharmacodynamic changes in agents affecting the central nervous system (CNS), cardiovascular, and endocrine functions. RESULTS: Older adults frequently demonstrate an exaggerated response to CNS-active drugs. This is in part due to an underlying age-related decline in CNS function and in part due to increased pharmacodynamic sensitivity for some benzodiazepines, anesthetics, and opioids. The most important pharmacodynamic differences with age for cardiovascular agents are the decrease in effect for beta-adrenergic agents. This decline in response in vascular, cardiac, and pulmonary tissue may be due to a decrease in Gs protein interactions. Most studies indicate there is no decrease in  $\alpha_1$ -receptor sensitivity with age. Angiotensin-converting enzyme inhibitors do not show age-related differences in elderly patients. With the dihydropyridine calcium channel blockers, there was a slight increase in effect for older adults, but this was only for treatment-naive patients and was transient. Nondihydropyridines did not show an age-associated change in pharmacodynamic effect; however, in the elderly, there appeared to be a decrease in the PR interval prolongation normally seen with these agents. Studies of diuretics indicated that the changes in diuretic and natriuretic effects seen in the elderly were associated with pharmacokinetic changes and were not pharmacodynamic in nature. There was a lack of consistent evidence regarding whether sulfonylureas show age-related changes in pharmacodynamic effect. CONCLUSIONS: There is a general trend of greater pharmacodynamic sensitivity in the elderly; however, this is not universal, and these age-related changes must be investigated agent-by-agent until further research yields greater understanding of the molecular mechanisms underlying the aging process.



- Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA, Kirshner MA, Sorisio DA, Bies RR, Gharabawi G. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc*. 2008 Jul;56(7):1333-41.

The objective of this study was to measure the anticholinergic activity (AA) of medications commonly used by older adults. A radioreceptor assay was used to investigate the AA of 107 medications. Six clinically relevant concentrations were assessed for each medication. Rodent forebrain and striatum homogenate was used with tritiated quinuclidinyl benzilate. Drug-free serum was added to medication and atropine standard-curve samples. For medications that showed detectable AA, average steady-state peak plasma and serum concentrations (C<sub>max</sub>) in older adults were used to estimate relationships between in vitro dose and AA. All results are reported in pmol/mL of atropine equivalents. At typical doses administered to older adults, amitriptyline, atropine, clozapine, dicyclomine, doxepin, L-hyoscyamine, thioridazine, and tolterodine demonstrated AA exceeding 15 pmol/mL. Chlorpromazine, diphenhydramine, nortriptyline, olanzapine, oxybutynin, and paroxetine had AA values of 5 to 15 pmol/mL. Citalopram, escitalopram, fluoxetine, lithium, mirtazapine, quetiapine, ranitidine, and temazepam had values less than 5 pmol/mL. Amoxicillin, celecoxib, cephalexin, diazepam, digoxin, diphenoxylate, donepezil, duloxetine, fentanyl, furosemide, hydrocodone,

lansoprazole, levofloxacin, metformin, phenytoin, propoxyphene, and topiramate demonstrated AA only at the highest concentrations tested (patients with above-average C(max) values, who receive higher doses, or are frail may show AA). The remainder of the medications investigated did not demonstrate any AA at the concentrations examined. Psychotropic medications were particularly likely to demonstrate AA. Each of the drug classifications investigated (e.g., antipsychotic, cardiovascular) had at least one medication that demonstrated AA at therapeutic doses. Clinicians can use this information when choosing between equally efficacious medications, as well as in assessing overall anticholinergic burden.



- ElDesoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. *Am J Ther.* 2007 Sep-Oct;14(5):488-98.

Aging is characterized by a progressive loss of functional capacities of most if not all organs, a reduction in homeostatic mechanisms, and a response to receptor stimulation. Also, loss of water content and an increase of fat content in the body are reported. Therefore, understanding the influence of age-dependent changes in composition and function of the body on the pharmacokinetics and pharmacodynamics of drugs is important before prescribing drugs to elderly patients. In this study, a Medline search for articles published in the period between 1975 and June 2006 was conducted with use of the key words aging, pharmacokinetics, and pharmacodynamics to review data related to alteration in pharmacokinetics and pharmacodynamics in elderly patients. Analysis of data revealed that the most important pharmacokinetic changes in old age include a decrease in the excretory capacity of the kidney more than the decline in the rate of hepatic drug metabolism. On the other hand, pharmacodynamic changes in the elderly are frequent and commonly ascribed to alteration in the sensitivity to drugs, irrespective of changes in drug disposition. For instance, the sensitivity of the cardiovascular system to beta-adrenergic agonists and antagonists decreases in old age, and the incidence of orthostatic episodes in response to drugs that lower blood pressure increases. However, the central nervous system becomes vulnerable in the elderly to agents that affect brain function (e.g., opioids, benzodiazepines, and psychotropic drugs). Therefore, these drugs must be used very cautiously in this age group. In conclusion, the complexity of the interactions between polypharmacy, comorbidity, altered pharmacodynamic sensitivity, and even modest changes in pharmacokinetics in elderly necessitate the medical approach "start low and go slow" for aged subjects, especially if drug therapy is considered beneficial or absolutely necessary for them.



- Jeste DV, Blazer D, Casey D, Meeks T, Salzman C, Schneider L, Tariot P, Yaffe K. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology.* 2008 Apr;33(5):957-70.

In elderly persons, antipsychotic drugs are clinically prescribed off-label for a number of disorders outside of their Food and Drug Administration (FDA)-approved indications (schizophrenia and bipolar disorder). The largest number of antipsychotic prescriptions in older adults is for behavioral disturbances associated with dementia. In April 2005, the FDA, based on a meta-analysis of 17 double-blind randomized placebo-controlled trials among elderly people with dementia, determined that atypical antipsychotics were associated with a significantly (1.6-1.7 times) greater mortality risk compared with placebo, and asked that drug manufacturers add a 'black box' warning to prescribing information for these drugs. Most deaths were due to either cardiac or infectious causes, the two most common immediate causes of death in dementia in general. Clinicians, patients, and caregivers are left with unclear choices of treatment for dementia patients with psychosis and/or severe agitation. Not only are psychosis and agitation common in persons with dementia but they also frequently cause considerable caregiver distress and hasten institutionalization of patients. At the same time, there is a paucity of evidence-based treatment alternatives to antipsychotics for this population. Thus, there is insufficient evidence to suggest that psychotropics other than antipsychotics represent an overall effective and safe, let alone better, treatment choice for psychosis or agitation in dementia; currently no such treatment has been approved by the FDA for these symptoms. Similarly, the data on the efficacy of specific psychosocial treatments in patients with dementia are limited and inconclusive. The goal of this White Paper is to review relevant issues and make clinical and research recommendations regarding the treatment of elderly dementia patients with psychosis and/or agitation. The role of shared decision making and caution in using pharmacotherapy for these patients is stressed.



- Rochon PA, Normand SL, Gomes T, Gill SS, Anderson GM, Melo M, Sykora K, Lipscombe L, Bell CM, Gurwitz JH. Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med.* 2008 May 26;168(10):1090-6.

BACKGROUND: Antipsychotic therapy is widely used to treat behavioral problems in older adults with dementia. Cohort studies evaluating the safety of antipsychotic therapy generally focus on a single adverse event. We compared the rate of developing any serious event, a composite outcome defined as an event serious enough to lead to an acute care hospital admission or death within 30 days of initiating antipsychotic therapy, to better estimate the overall burden of short-term harm associated with these agents. METHODS: In this population-based, retrospective cohort study, we identified 20 682 matched older adults with dementia living in the community and 20 559 matched individuals living in a nursing home between April 1, 1997, and March 31, 2004. Propensity-based matching was used to balance differences between the drug exposure groups in each setting. To examine the effects of antipsychotic drug use on the composite outcome of any serious event we used a conditional logistic regression model. We also estimated adjusted odds ratios using models that included all covariates with a standard difference greater than 0.10. RESULTS: Relative to those who received no antipsychotic therapy, community-dwelling older adults newly dispensed an atypical antipsychotic therapy were 3.2 times more likely (95% confidence interval, 2.77-3.68) and those who received conventional antipsychotic therapy were 3.8 times more likely (95% confidence interval, 3.31-4.39) to develop any serious event during the 30 days of follow-up. The pattern of serious events was similar but less pronounced among older adults living in a nursing home. CONCLUSIONS: Serious events, as indicated by a hospital admission or death, are frequent following the short-term use of antipsychotic drugs in older adults with dementia. Antipsychotic drugs should be used with caution even when short-term therapy is being prescribed.



- Wright RM, Roumani YF, Boudreau R, Newman AB, Ruby CM, Studenski SA, Shorr RI, Bauer DC, Simonsick EM, Hilmer SN, Hanlon JT; Health, Aging and Body Composition Study. Effect of central nervous system medication use on decline in cognition in community-dwelling older adults: findings from the Health, Aging and Body Composition Study. *J Am Geriatr Soc.* 2009 Feb;57(2):243-50.

OBJECTIVES: To evaluate whether combined use of multiple central nervous system (CNS) medications over time is associated with cognitive change. DESIGN: Longitudinal cohort study. SETTING: Pittsburgh, Pennsylvania, and Memphis, Tennessee. PARTICIPANTS: Two thousand seven hundred thirty-seven healthy adults (aged > or =65) enrolled in the Health, Aging and Body Composition study without baseline cognitive impairment (modified Mini-Mental State Examination (3MS) score > or =80). MEASUREMENTS: CNS medication (benzodiazepine- and opioid-receptor agonists, antipsychotics, antidepressants) use, duration, and dose were determined at baseline (Year 1) and Years 3 and 5. Cognitive function was measured using the 3MS at baseline and Years 3 and 5. The outcome variables were incident cognitive impairment (3MS score <80) and cognitive decline (> or =5-point decline on 3MS). Multivariable interval-censored survival analyses were conducted. RESULTS: By Year 5, 7.7% of subjects had incident cognitive impairment; 25.2% demonstrated cognitive decline. CNS medication use increased from 13.9% at baseline to 15.3% and 17.1% at Years 3 and 5, respectively. It was not associated with incident cognitive impairment (adjusted hazard ratio (adj HR)=1.11, 95% confidence interval (CI)=0.73-1.69) but was associated with cognitive decline (adj HR 1.37, 95% CI=1.11-1.70). Longer duration (adj HR=1.39, CI=1.08-1.79) and higher doses (>3 standardized daily doses) (adj HR=1.87, 95% CI=1.25-2.79) of CNS medications suggested greater risk of cognitive decline than with nonuse. CONCLUSION: Combined use of CNS medications, especially at higher doses, appears to be associated with cognitive decline in older adults. Future studies must explore the effect of combined CNS medication use on vulnerable older adults.



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*Next Month's Issue:*

Fall Prevention

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