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# UPDATE

THE PREMIER MONTHLY FORUM ABOUT THE USE OF PSYCHOTROPIC MEDICATIONS IN THE ELDERLY

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## Highlights...

This month's top story is a special report on substance abuse in the elderly. Diagnosis is often the biggest challenge in this population in particular and we examine screening and intervention practices, as well as looking specifically at the growing abuse of prescription drugs and alcohol.

Also, a new open-label study shows that there may be some potential for lithium as a modification therapy for Alzheimer's disease, though high discontinuation rates might impact its long-term use.

## Inside

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### SPECIAL REPORT

## Substance abuse and the aging brain: Screening, diagnoses and treatment

**S**ubstance abuse in older adults and its effects on the aging brain may often be misdiagnosed as a function of normal aging or underlying medical conditions. Although increased problems with sleep, memory or

falling can be a consequence of older age, they can also be warning signs of drug abuse. The lack of validated screening instruments for substance abuse in the elderly compounds the problems of diagnosis and treatment.

In a review "Drugs of abuse and the aging brain," published in the February 2008 issue of *Neuropsychopharmacology*, Gayathri J. Dowling, PhD, and colleagues from the National Institute on Drug Abuse (NIDA) indicate that alcohol and prescription drugs are the most commonly abused substances among older patients.

One worrying trend is the increase in illicit drug use among adults over the age of 50, a pattern which may reflect, at least in part, an aging baby boomer generation. Citing figures from the National Survey on Drug Use and Health

**SUBSTANCE ABUSE**, continued on page 4

## précis

- Recognizing drug abuse in the elderly may be challenging as the symptoms can often be mistaken as a function of normal aging or underlying medical conditions; validated screening instruments for substance abuse are relatively scarce, compounding the problems of diagnosis and treatment
- Addressing these critical issues, researchers from the National Institute on Drug Abuse and from the Peter Lamy Center on Drug Therapy and Aging at the University of Maryland-Baltimore, contribute their insights into the growing problem of drug abuse in the baby-boomer generation

### ALZHEIMER'S DISEASE

## Study shows lithium should be explored as modification therapy for Alzheimer's

**I**n a study published in the *International Journal of Geriatric Psychiatry*, researchers were able to recruit 22 elderly people with AD to determine the safety and feasibility of using lithium to treat the disease.

While ratings on the Lithium Side Effects Rating Scale did not differ significantly between those who remained in the study and those who dropped out early, discontinuation rates were high (14 of 22 patients dropped out early). Because the side effects were few and relatively mild, the authors conclude that lithium should be explored as a modification therapy for AD. But high discontinuation rates may pose challenges for lithium's long-term use.

**LITHIUM**, continued on page 6

## précis

- An open-label study to assess the safety and feasibility of long-term prescribing of lithium for treatment of Alzheimer's disease (AD) enrolled 22 people and a control group
- Fourteen participants discontinued after a mean of 16 weeks during the 39-week study; side-effect reports on the Lithium Side Effects Rating Scale did not differ between those leaving the study and those remaining in the study
- While side effects were relatively few, mild, and reversible, discontinuation rates were high; the use of lithium as a potential disease modification therapy for AD should be explored further, though it does present problems

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## Greater risk of pneumonia associated with antipsychotic use in the elderly

### précis

• Elderly patients may have a significantly higher risk of developing pneumonia while taking antipsychotic medications, according to a large-scale case-control study; the risk was highest during the first week after starting an antipsychotic and was higher among patients taking atypicals rather than older antipsychotics

**A** large-scale case-control study has found a nearly 60% increased risk of pneumonia associated with current use of antipsychotics in elderly patients. The risk of developing pneumonia was highest during the first week after starting an antipsychotic, and higher among users of atypicals rather than conventional antipsychotics. No clear dose-related association was found.

According to the investigators, the relationship between antipsychotics and the development of infections, particularly pneumonia, is unclear, and the pathophysiological mechanisms behind the putative relation has not been investigated. One hypothesis is that blocking of dopamine receptors may result in dyskinesia “of the oral pharyngeal musculature, rigidity, and spasm of the pharyngeal musculature, which can result in aspiration.” Another possible mechanism is xerostomia or dryness of the mouth as it may lead to impaired oropharyngeal bolus transport. Xerostomia can also result from the use of antipsychotics with significant anticholinergic activity. Sedation is also known to be a cause of swallowing problems caused by histamine-1-receptor blocking in the cen-

tral nervous system.

The aim of the current study was to investigate the association between antipsychotic use in elderly patients and the risk of pneumonia using a nested case-control study design.

### Study details

Using pharmacy dispensing records from community pharmacies of approximately 950,000 community-dwelling residents in the Netherlands from 1985 onwards, 22,944 elderly patients were identified as having received at least one antipsychotic prescription between April 1985 and December 2003, among whom 543 were identified as having been hospitalized for pneumonia. Each of the hospitalized cases was matched with 4 controls of patients not hospitalized for pneumonia. All patients were followed up until they had developed any type of pneumonia, had died, or until the end of the study period.

Among current users of antipsychotics, users of atypicals (risperidone, olanzapine, clozapine, and quetiapine) were distinguished from users of older agents and users concurrently using more than one antipsychotic agent. Potential confounders included the use of drugs and the presence of medical conditions previously associated with the risk of pneumonia.

### Results

The analysis was based on 543 elderly patients (age  $\geq 65$  years) who developed pneumonia matched with 2,163 controls. A total of 65 cases (12%) were diagnosed as aspiration pneumonia and 478 cases (88%) as other pneumonia. Delirium was slightly more prevalent among cases than controls, and the number of hospital admissions and prescribed drugs also higher among cases compared with controls.

Current antipsychotic use, but not past use, was associated with a 60% greater risk of pneumonia (adjusted odds ratio [OR] =

1.6; 95% confidence interval [CI] = 1.3-2.1]. Secondary analyses, excluding elderly people diagnosed with delirium during hospital admission, showed a corresponding estimate for pneumonia in the remaining patients as 1.9 (95% CI = 1.6-2.4). Excluding elderly people who had used antibiotics or benzodiazepines one week prior to hospital admission, the estimated risk of pneumonia was 1.8 (95% CI = 1.4-2.3), and 1.9 (95% CI = 1.5-2.3), respectively.

During the first week of antipsychotic use, the risk of developing pneumonia was nearly 5 times greater. With longer use of antipsychotics the risk of pneumonia decreased, and no effect of a prescribed daily dose was found.

Most of the current users of antipsychotics (83%), were prescribed conventional agents, 15% were prescribed an atypical (mostly risperidone), and 2% a combination. Although there was a stronger association between atypical antipsychotic use and pneumonia, the number of patients using atypicals was relatively small.

### Clinical implications

The authors conclude that although the mechanism between antipsychotic use and pneumonia remains speculative, these drugs should not be overlooked as a possible cause of pneumonia in elderly patients. Although antipsychotic-induced dysphagia, which has only been described in case reports, is not well known or possibly under-reported, clinicians should monitor elderly patients taking antipsychotics for sedation, decreased cough reflex and swallowing disorders, particularly as these symptoms are important risk factors for community-acquired pneumonia. ■

Knol W, van Marum RJ, Jansen PA, et al.: Antipsychotic drug use and risk of pneumonia in elderly people. *J Am Geriatr Soc* 2008 Feb 7; E-pub ahead of print: DOI: 10.1111/j.1532-5415.2007.01625.x. E-mail: r.j.vanmarum@umcutrecht.nl.

## SUBSTANCE ABUSE

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(2007) Substance Abuse and Mental Health Services Administration, Dowling and colleagues told *The Update* that illicit drug use has risen from 3.4% in 2002 to 6% in 2006 among adults aged 50 to 54 years. Such increases will result in greater demand for substance abuse treatment services for the elderly. The number of older adults who will

need such services is estimated to increase from 1.7 million in 2000 and 2001 to 4.4 million in 2020 (Gfroerer et al., 2003).

### Effects of drug abuse on the aging brain

Given the age-related changes in neurotransmitter systems that mediate the effects of drugs in the brain, even moderate drug abuse may present greater risks to

older adults, sometimes with devastating consequences, write Dowling and colleagues. Although there is clear evidence that the brain continues to change throughout life, there is little understanding of how drugs of abuse interact with these age-related changes. Given the dynamic nature of the brain, the use of drugs of abuse in older adults “may have unique consequences that influence drugs’ effects

in the brain and the treatment of substance abuse in this population," they write.

Chronic abuse of some drugs, such as cocaine, may exacerbate normal age-related changes in the brain, write Dowling and colleagues. Between the ages of 20 and 50, the maturation of frontal and temporal lobe white matter appears to be arrested in chronic users of cocaine. The natural decline in white matter after age 50 may therefore be more dramatic in cocaine users than in the healthy, aging, general population.

Some neuroprotective properties of nicotine and marijuana have been reported, although the adverse health effects of these drugs may outweigh their potential benefits, write Dowling and colleagues. Nicotine has been associated with a lower incidence of Parkinson's disease (PD). Other components of cigarette smoke have been shown to decrease monoamine oxidase B activity in the brain which may contribute to a lower incidence of PD. Marijuana has been reported to protect against neuronal damage caused by oxidation and inflammation, both of which are prevalent in aging, possibly contributing to adverse age-related health conditions such as PD, Alzheimer's disease, and cardiovascular disease. A better understanding of the mechanisms of these drugs can lead to more targeted pharmacotherapies to prevent and/or treat the myriad of diseases associated with aging, write Dowling and colleagues.

### Warning signs of drug abuse

Linda Simoni-Wastila, PhD, a researcher specializing in the area of prescription drugs, told *The Update*, "Identifying substance use problems in older adults is a tricky business because this population often has other frailties and vulnerabilities that require differentiation, including medical conditions that mimic symptoms of abuse, medication side effects, and psychiatric and cognitive impairments. Unfortunately, there are few appropriate screening or assessment tools for this population."

Simoni-Wastila is Associate Professor, School of Pharmacy, Department of Pharmaceutical Health Services Research, and Director of the Long-Term Care Initiative, Peter Lamy Center on Drug Therapy and Aging, University of Maryland-Baltimore.

### Psychotropic drugs

Substance abuse and comorbid psychiatric disorders are relatively common in younger and older adults, write Dowling

## Commentary: Diagnosing and treating drug abuse in the elderly

Addressing some of the problems in diagnosing and treating drug abuse in the elderly, Gayathri J. Dowling, Ph.D., Deputy Chief, Science Policy Branch, Office of Science Policy and Communications (OSPC), Susan R.B. Weiss, Ph.D., Chief, Science Policy Branch, OSPC, and Timothy P. Condon, Ph.D., Deputy Director, NIDA, contributed the following comments to *The Update*:

Diagnosing drug abuse among older adults is complicated by many factors. For example:

- Because substance abuse is predominantly perceived to be a disease of youth, physicians may have a bias against recognizing or attributing problems among their older patients to substance abuse.
- There is a relative lack of diagnostic criteria and/or screening instruments developed and tested in this age group. Some DSM-IV criteria for substance dependence, such as tolerance and activity reduction, for example, may not apply to this population.
- Warning signs of drug abuse (e.g., sleep problems, falls, memory problems) may be confused with or masked by concurrent physical and/or mental illnesses, or attributed to normal aging.
- Drug abuse may be problematic in elderly patients even when it doesn't reach the level of abuse or addiction.
  - Moderate levels of drug abuse could complicate comorbid conditions of aging or result in harm-

ful interactions with medications to threaten these disorders.

- Because of age-related changes in drug metabolism and the neurotransmitter systems mediating drug effects in the brain, moderate drug abuse may pose greater risks in older adults.

Addiction treatments have not been specifically designed or tested in elderly patients. However, once in treatment, older adults have outcomes equivalent to or better than those of younger adults, suggesting that the primary barrier to recovery is diagnosis and treatment entry. Still older patients may fare even better in programs tailored to them:

- Reflecting age-related brain changes, differences in the types of drugs abused in this population, and in the settings in which they are abused.
- Using supportive and non-confrontational approaches, cognitive behavioral therapy (for those not cognitively impaired) addressing negative affect, improving social support, and involving specially trained providers.
- Pharmacological therapies could also be a critical component of drug treatment in older adults. However, those currently available to treat substance abuse (e.g., bupropion, naltrexone, methadone, buprenorphine), have not been tested in older adults; thus, it is unclear if they retain their effectiveness or have unique adverse effects in this population.

and colleagues. Benzodiazepines are associated with cognitive decline and depression when used long-term, while stimulants may help to improve age-related cognitive deficits. Cardiovascular problems may be exacerbated by cocaine and amphetamine which may lead to myocardial infarctions and arrhythmias. The long-term use of these drugs can result in predisposition to cardiomyopathy, ventricular hypertrophy and premature atherosclerosis. Cocaine, crack and psychedelic drugs have all been reported to increase the risk of kidney disease. Potentially fatal complication of diabetes has been reported in cocaine abusers. Comorbid drug abuse also

raises the risk of falls and accidents that often result in hip fractures in the elderly.

### Alcohol

CAGE (Cut Down, Annoyed, Guilty, Eye-opener), a screening tool for alcohol abuse, has been evaluated in several studies for use in the elderly. Although the overall specificity and sensitivity of the questionnaire are considered satisfactory, CAGE is not considered quite as effective in eliciting information about past drinking problems and current drinking. Since elderly patients are prone to self-medication, "it is particularly important to modi-

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fy the CAGE questionnaire to detect drug abuse,” and for clinicians to remain aware that cognitive impairment can affect the patient’s ability to respond to the questions accurately. (Mersey, 2007)

Clinicians can (and should) screen their geriatric patients for potential drinking problems using either the CAGE or the Michigan Alcoholism Screening Test-Geriatric version (MAST-G), said Simoni-Wastila.

The American Geriatrics Society also provides detailed clinical guidelines for screening and interventions on alcohol use disorders in older adults: [www.americangeriatrics.org/products/positionpapers/alcohol.shtml](http://www.americangeriatrics.org/products/positionpapers/alcohol.shtml).

## Prescription drug abuse and polypharmacy

The disproportionate amount of prescription drugs consumed by elderly patients raises the risk of potentially severe drug-drug and drug-disease interactions. Complications may arise from unintended misuse of a prescription drug (e.g., unintentional double dosing) or intended abuse of a drug whether or not required for a medical condition (e.g., taking higher doses of drugs prescribed for chronic pain, anxiety or insomnia).

Because there are no tools to assess drug use in the elderly, particularly prescription drug abuse, which is especially problematic in older adults, frank discussions are necessary. Providers need to ask elderly patients about all medications they may be using, side effects, frequency of use and dose, and where they obtain the medications, said Simoni-Wastila. Questions about non-prescription drugs and

supplements are also important as many of these substances contain alcohol or mood-altering substances such as kava.

Providers need to prod for other potential abuse problems, said Simoni-Wastila, and to ask frankly about patients’ illicit substance use, alcohol consumption patterns and preferences, particularly when taking medications such as benzodiazepines, which are cross-tolerant with alcohol.

Some of the warning signs she said are excessive worrying by the patient about whether their psychotropic drugs are really working; having a particular attachment to their medication and detailed knowledge of its effects; continued use of a drug and requests for refills after the condition for which the drug was prescribed has been resolved; complaints about physicians who reduce or taper dosages without supervision, who refuse to write prescriptions for preferred drugs, or who do not take symptoms seriously; excessive sleeping, especially during the day; social withdrawal; and changes in grooming and hygiene.

## Risk factors & prescribing patterns

In an article on the use of psychotropic drugs in older adults, Simoni-Wastila & Yang (2006) indicate that older women appear to be particularly at risk of prescription drug abuse. Compared with their male peers, older women are prescribed and consume more psychotropic medications, benzodiazepines in particular, and are more likely to be long-term users of these substances.

Other risk factors for prescription drug abuse in the elderly include social isolation, poor health status, polypharmacy, chronic medical comorbidity, and previous and/or co-occurring substance use or psy-

chiatric disorder.

Physician specialties also play a role in influencing prescribing patterns, with primary care physicians prescribing more psychotropic drugs of all classes, including minor tranquilizers and opioid analgesics, compared with specialists.

## Conclusions

Dowling and colleagues indicate that there is significant reason to believe that as the number of adults with substance abuse increases, so may the prevalence of older patients with drug-disease complications, although how such abuse impacts the common illnesses that occur during aging remains poorly understood.

New research efforts, including brain imaging studies throughout the lifespan and clinical trials, and heightened awareness among health care professionals and the general public, will contribute to a better understanding of the long-term effects of drug abuse in older adults. ■

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### FURTHER READING

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## LITHIUM

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### Background

Alzheimer’s Disease (AD) affects over 24 million people worldwide. There are no disease modifying therapies, but two therapeutic targets have been identified. The first is amyloid, the peptide that aggregates in the neuritic plaque. Compounds designed to modify the aggregation of amyloid are in development. Another potential therapeutic target for AD is the neurofibrillary tangle, formed from aggregated and phosphorylated tau protein. Reducing the phosphorylation of tau through inhibition of the relevant

kinase is one therapeutic approach, note the study authors, led by Simon Lovestone and Alastair Macdonald of the Institute of Psychiatry, King’s College, London.

According to the authors, evidence suggests that glycogen synthase kinase-3 (GSK-3) is the predominant tau-kinase in the brain. Lithium is a GSK-3 inhibitor. Partial GSK-3 inhibition is likely to be achieved during therapy. Rat and rabbit studies indicate that lithium might prevent progression from amyloid-related pathology to neurodegeneration. These data suggest that lithium might be a disease-modifying therapy for AD.

However, studies have yielded mixed

results on the question of whether long-term lithium users are at lower risk for AD. While Terao et al (2006) found that psychiatric patients who had ever taken lithium had a higher MMSE score than those who had never taken lithium, and Nunes et al (2007) found lower rates of dementia among bipolar disorder patients treated with lithium, a third study (Dunn et al 2005) found a slightly higher risk of dementia in patients taking lithium.

Lithium has a narrow therapeutic window and known neurotoxic side effects, as well as interactions with other drugs. These factors might limit the usefulness of lithium for AD. This study assessed the feasi-

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