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**Editor:**  
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## Highlights...

This month we take a look at treatment for dually diagnosed elderly patients. A new study examines whether naltrexone can benefit patients with both depression and alcohol dependence.

We also have several articles focused on the latest treatments for Parkinson's disease in this month's issue. Along with the lead story on rasagiline on page 1, which includes our At A Glance feature on pages 6 and 7, see also pages 3 and 8.

## Inside

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## SUBSTANCE ABUSE IN THE ELDERLY

# Curbing drinking alleviates depression in dually diagnosed seniors

## Study examines effectiveness of naltrexone plus SSRI

**T**o get clear answers about how to treat an illness, researchers often seek "pure" cases untainted by additional maladies. Unfortunately, the answers they get may not relate to the real world, where patients' problems frequently come in messier packages.

For instance, clinical trials of antidepressants often exclude people with substance abuse disorders. According to Ismene Petrakis, M.D., an associate professor of psychiatry at the Yale University School of Medicine who directs the substance abuse program at the Veterans Affairs (VA)

## précis

- Randomized, placebo-controlled study of 74 outpatients (55 years and older) with alcohol dependence and major depression
- After detox, patients received either naltrexone or placebo; all participants also took 50 mg sertraline
- The two treatment groups showed similar rates of depression remission, lack of drinking relapse, or both suggesting a lack of treatment effect for naltrexone

Connecticut Healthcare System in West Haven, studies tend to look at either depression or alcohol dependence but not both.

Petrakis told *The Update* that research has found higher rates of depression in people

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## PARKINSON'S DISEASE

# Rasagiline may improve symptoms in Parkinson's disease patients

## Increased dyskinesia also observed

**A**ccording to the results of two randomized, placebo-controlled trials — the PRESTO<sup>1</sup> and LARGO<sup>2</sup> studies — researchers suggest that rasagiline (Agilect, pending FDA approval), a new monoamine oxidase type b (MAO-B) inhibitor, may improve motor fluctuations, reducing off time in levodopa-treated patients with Parkinson's disease (PD). However, in the PRESTO study, investigators also observed increased dyskinesias in the rasagiline-treated group compared with the placebo group.

During sustained levodopa therapy, patients with PD may undergo motor dys-

## précis

- Results from the PRESTO and LARGO trials investigating safety and efficacy of rasagiline in levodopa-treated patients with Parkinson's disease
- Randomized, placebo-controlled trials suggest rasagiline may improve motor fluctuations and symptoms in patients with early and advanced stages of PD
- Increased dyskinesias were also observed in rasagiline-treated subjects compared with placebo in the PRESTO study

function that can be as debilitating as the underlying illness. Although levodopa is generally considered to be the treatment of choice

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## DRINKING AND DEPRESSION

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with alcohol dependence than in those without, and elevated rates of alcohol dependence in people with depression compared to the general population. "In real clinical practice," she said, "a lot of what you see is people who have both."

A trickle of studies has begun evaluating potential treatment strategies for these dual-diagnosis patients. David Oslin, M.D., of the University of Pennsylvania School of Medicine, where he is an associate professor, and the Philadelphia VA Medical Center, noted that despite "fairly consistent results" showing that selective serotonin reuptake inhibitors (SSRIs) can relieve their mood problems, it remains unclear whether they can diminish drinking.

In a recent paper, Oslin bemoaned the lack of randomized trials testing combined treatments for alcohol dependence and depression in comorbid patients. To address this gap, he launched a study of whether naltrexone, an opioid-receptor antagonist that helps prevent drinking relapses, would reduce their drinking and depression, when used with the SSRI sertraline and psychosocial treatment.

Some experts have written that heavy drinking undermines depression treatment, and Oslin said that clinicians often overlook drinking in older patients. Consequently, his study explored whether alcohol use during treatment would correlate with poorer depression outcomes.

### Study details

The trial enrolled 74 outpatients, age 55 years and older (mean age of 63 years), who met DSM-IV criteria for alcohol dependence and major depression. They showed no signs of recent opioid use or dependence on psychoactive substances other than alcohol or nicotine.

After completing alcohol detoxification, study participants were randomly assigned to receive either placebo or naltrexone (ReVia), in a block design stratified by gender and recruitment site. In addition, all received psychosocial therapy designed to enhance treatment adherence.

After a week on either placebo or a 50-mg daily dose of naltrexone, all participants also began taking 50 mg sertraline (Zoloft) per day. After the first week, their antidepressant dose jumped to 100 mg as tolerated. Treatment and follow-up contin-

ued for 12 weeks.

BRENDA, the acronym for the psychosocial therapy, stands for Biopsychosocial evaluation, Report to the patient on the assessment, Empathetic approach to the patient's situation, Needs assessment, Direct advice to patient on how to meet those needs, and Assessment of the patients' progress. A nurse led the 20-to-30-minute sessions, which transpired weekly for the first eight weeks and biweekly thereafter.

To gauge adherence, the nurse tracked patients' attendance at therapy sessions. Pill counts and patients' self reports indicated compliance with the medication regimen.

At each visit, the study assessed the severity of patients' depression using the Hamilton Rating Scale for Depression (Ham-D), as well as the frequency and amount of drinking via the Timeline Followback method. The latter used a calendar to obtain reports of drinking for the 90 days before detoxification and during treatment. Amounts of alcohol were recorded in standard drinks, defined as 12 ounces of beer, 6 ounces of wine, or 1-1/2 ounces of hard liquor.

The main indicators of treatment response were depression remission, defined as a Ham-D score below 10, and relapse to heavy drinking; downing more than 4 standard drinks in one day for men or 3 for women, comprised a relapse. On average, they had been drinking to the point of intoxication for 17 years. They consumed an average of 11 drinks per drinking day and drank heavily on 68% of the 90 days before detoxification.

Over half (51%) had never received formal treatment for alcohol dependence,

although 30% had entered treatment more than once. Over a fourth (27%) of participants had received outpatient mental health treatment, 26% were already taking an antidepressant, and 8% had attempted suicide.

### Results

After 12 weeks in the study, 53% of participants were in remission from their depression. Two-thirds (66%) had avoided relapsing into heavy drinking; 49% had totally refrained from drinking during the study.

Contrary to expectations, the two treatment groups showed similar rates of depression remission, lack of drinking relapse, or both. They achieved equivalent abstinence rates as well as equally high rates of adhering to the treatment.

To explain the lack of treatment effects for naltrexone, Oslin cited the low rates of relapse, even in the placebo group. Referring to the naltrexone, he said, "A lot of these patients did eliminate their drinking without the medicine and so it was really hard to show an added benefit."

Many patients complained of adverse events, with 58% reporting headache, 51% anxiety, 42% nausea, 39% impaired sexual functioning, and 24% vomiting. Each of these symptoms occurred as often in those taking placebo as in the naltrexone group.

A post-hoc analysis suggested possible gender differences in treatment response ( $p=0.048$ ). Among the women, 25% in the naltrexone group responded favorably, compared to 71% in the placebo group. In men, 45% improved on naltrexone and 37% on placebo. Oslin said that even though this study found similar adverse event rates in men and women, others have found greater naltrexone toxicity in women.

### Drinking and depression remission

As for the impact of drinking during treatment on depression outcomes, analyses showed that any relapse to heavy drinking was associated with reduced likelihood of a depression remission (OR=3.83, 95% CI=1.36 to 10.81) or symptom relief ( $p=0.013$ ). Those with more frequent drinking binges were less likely to have a depression remission (OR=2.29, 95% CI=1.34 to 3.90) or decreased symptoms ( $p<0.001$ ).

Another post-hoc test found that patients who consumed any alcohol on

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**After 12 weeks in the study, 53% of participants were in remission from their depression. Two-thirds (66%) had avoided relapsing into heavy drinking; 49% had totally refrained from drinking during the study.**

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more than 2 days during the study showed a poorer response of their depression to treatment than those who drank on 2 or fewer days (OR=4.00, 95% CI=1.44 to 10.82). On the other hand, complete abstinence did not help depression outcomes.

According to Oslin, the study shows that “older adults do very, very well in substance abuse treatment,” perhaps due to their high adherence rates. In his study, 83% of participants completed the psychosocial treatment. The patients took sertraline on 79% of study days and either naltrexone or placebo on 83%.

## “The study shows that older adults do very, very well in substance abuse treatment.”

David Oslin, M.D.

While getting patients to stop or substantially reduce their drinking wasn't difficult, Oslin said, “the depression was quite another story.” After 3 months in treatment, nearly half remained depressed, despite psychotherapy, antidepressant medicine, and stopping or curtailing their drinking.

Petrakis warned against overgeneralizing from naltrexone's failure to improve depression or drinking in comorbid patients in this one study. She said, “I wouldn't want to prematurely say that naltrexone is not effective in this population.”

To explain why giving up alcohol might aid depression treatment, Oslin surmised that a patient “sitting at the dinner table with a glass of wine and the pill bottle” might not choose the antidepressant. In addition, he noted, “There are a couple of hints in the literature that alcohol may change the pharmacokinetics of certain antidepressants.”

Both Oslin and Petrakis stressed that the findings underscore the need to simultaneously treat both depression and alcohol dependence in patients suffering from them. As Oslin put it, “Only in the mental health field do we kind of soft-pedal into treatment.”

Oslin DW: Treatment of late-life depression complicated by alcohol dependence. *Am J Geriatr Psychiatry* 2005; 13(6):491-500. E-mail: oslin@mail.med.upenn.edu.

## Letter to the Editor

### Availability of benzodiazepines to be curtailed

A recent article in *The Update* (July 2005), reviewing an analysis by Heather Ashton, M.D., discussed the uses, misuses, and treatment ranges of benzodiazepines. The article was accompanied by a précis that noted “Potential trauma of benzodiazepine withdrawal can be avoided using gradual dosage tapering and psychological support.” The gradual tapering may take many months, in some cases, and which for some, in the United States specifically, may be rapidly dwindling as a result of the Medicare Modernization Act.<sup>1</sup>

On January 1, 2006, benzodiazepines as a class will be forbidden coverage by any Prescription Management Plan that provides standard coverage to the Medicare population or to the dual-eligible population that will be enrolled in this new benefit, losing their previous Medicaid coverage. As this is the result of a congressional act, the CMS (Centers for Medicare and Medicaid Services) is unable to effect any modification to this categorical exclusion. Several other classes, including barbiturates, are likewise affected.

Many have written letters to CMS during the comment period, but the final regulations are clear that congressional action is the only way, barring action by the Secretary of HHS, to resolve this potential problem. The American Society of Consulting Pharmacists released a brief on the exclusion I mid-2004.<sup>2</sup> Richard Stefanacci (Executive Director of the Health Policy Institute of the University of the Sciences in Philadelphia) has written on the costs of the exclusion of benzodiazepines, and the Medicare Rights Center has just released an overview of the problem which expands on his comments.<sup>3,4</sup> Scant reference exists elsewhere within the public press or the medical press. Significant public and professional awareness-raising is necessary. Additional information is available at <http://www.noemaine.org/benzo/benzo.htm>.

Though CMS articulates that states may elect to provide so-called wrap-around coverage, this is not certain and again not something about which there has been much publicity. In Illinois the restriction of benzodiazepines for Medicaid recipients to 8 doses a month has likewise received little attention even within the state.

Each state and territory and the District of Columbia must make a decision as to how to approach this exclusion on a financial, policy, and public health set of calculations, bearing in mind the difficulty in weaning many patients, the limited time left, and the estimated size of affected patients at 1.7 million across the US. Clinicians must make decisions about their individual patients based on the likelihood or not that Congress will address this, and that their particular state will set a policy. And patients need to be educated about the current situation in order to make informed decisions about their pharmacological care.

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#### Editor's note:

In a press release issued on July 1, 2005 the American Psychiatric Association (APA) thanked Benjamin L. Cardin (D-MD) for introducing legislation to repeal the current law that excludes coverage of benzodiazepines from Medicare's new prescription drug benefit. The APA also commended Rep. Jim Ramstad (R-MN) for his role as the lead cosponsor of the legislation. The American Medical Association (AMA) and National Alliance of the Mentally Ill (NAMI) also publicly indicated strong support for this legislation. [[www.psych.org](http://www.psych.org)]

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