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Highlights...

Jason Karlawish, M.D., discussed with us his groups' new research about whether patients with Alzheimer's are competent to make their own treatment decisions. The results are not as cut and dry as you might expect.

Our other top story focuses on how to **diagnose and manage benzodiazepine dependence and withdrawal** — a key topic bearing in mind upcoming changes in Medicaid eligibility.

Inside

THE DOUBLE-EDGED SWORD

Gauging competency of patients to decide treatment for Alzheimer's disease

Advances in the early detection of Alzheimer's disease (AD) raise challenges for health care professionals who must determine whether patients remain capable of giving informed consent for treatment. They cannot simply assume that patients, particularly those with early-stage dementia, lack the ability to decide their treatment, nor should they presume they retain that ability, according to Jason Karlawish, M.D., assistant professor of medicine and associate director of the Memory Disorders Clinic at the University of Pennsylvania.

In fact, Karlawish warned that clinicians who misread patients' decision-making abilities could "run ragged over their rights" or "let them exercise rights that they're not capable any more of exercising," raising the chances that patients will make decisions against their own best interests. "You see the double-edged sword?" he said.

Despite the high stakes, clinicians who treat AD have had little data to guide them in determining competency. As Karlawish and colleagues wrote in their recent paper in the jour-

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précis

- Semistructured in-home interviews of 48 patients with mild to moderate Alzheimer's disease and 102 family caregivers of patients to study treatment decision-making ability
- Insight/awareness of illness was associated with retaining the ability to make decisions

BENZODIAZEPINES

What are the risks of long-term use? Diagnosing and managing dependency

Although the American Psychiatric Association (APA) recommends that benzodiazepines are used best in time-limited situations, the APA reports that one benzodiazepine user in four remains on these agents for a year or longer. A high prevalence of long-term benzodiazepine use among the elderly puts this particular population at increased risk of dependence, especially for those who are institutionalized.

As the risk of benzodiazepine dependence increases with age, an understanding of the consequences of long-term use and the potential for dependence is crucial for patient management, including pharmacological as well as non-pharmacological treatment options.

We spoke with C. Heather Ashton, DM (Emeritus Professor of Psychopharmacology, School of Neurosciences, Department of Psychiatry, University of Newcastle upon Tyne, UK), who suggests that doctors, psychi-

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précis

- Expert discusses the risks of benzodiazepines, and offers guidance on avoiding dependence
- Potential trauma of benzodiazepine withdrawal can be avoided using gradual dosage tapering and psychological support
- Depression, isolation and chronic pain predispose the elderly to benzodiazepine use, with the risk of dependence increasing with age

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study on safety and tolerability data from a 28-day open-label, multicenter prospective trial carried out between August 2002 to August 2003. These results are compared with data on adverse events from a retrospective pivotal, placebo-controlled trial of AD patients who had not been previously treated with ChE inhibitors.

The subjects were allowed to continue most medications except for nootropics, lithium, anticholinergics and medication for Parkinson's disease. Exclusion criteria included previous exposure to rivastigmine, sensitivity to donepezil, and intake of an investigational drug 30 days prior to screening.

Approximately 14 days prior to baseline, subjects were screened and allowed to continue their daily dose of donepezil. Their last dose of donepezil was taken either the evening before or on the morning of their baseline visit (day 0). The first dose of rivastigmine (1.5 mg) was given on study day one, 24 to 36 hours after their last donepezil dose. A 1.5-mg dose (twice daily) was maintained for 28 days. For patients unable to tolerate this dose, rivastigmine was decreased to 1.5 mg once a day for up to 3 days, after which twice daily dosing was reinitiated. Vital signs remained stable throughout the study period for all subjects.

In the open-label study, 58 (out of 61) patients (mean age=76.2 years; 33 females) completed 4 weeks of rivastigmine treatment with no suspected drug-related discontinuations during this period. The reasons for early study drop-out were irritability, confusion, vomiting and, in 1 patient, worsening social withdrawal with verbal perseveration. Overall gastrointestinal adverse events were seen in 8.2% of subjects at day 7, and in 11.5% at day 28.

The authors conclude that "switching patients with Alzheimer's disease from donepezil to rivastigmine is well tolerated. Results are similar to initiation of rivastigmine in previously untreated patients. Immediate transition from one agent to another is preferred…Moreover, switching to another ChE inhibitor may positively impact symptoms of Alzheimer's disease." ■

* Funding sources not indicated.

Sadowsky CH, Farlow MR, Atkinson L, et al.: Switching from donepezil to rivastigmine is well tolerated: results of an open-label safety and tolerability study. *Prim Care Companion J Clin Psychiatry* 2005; 7(2):43-48. E-mail: chsadow@aol.com.

THE DOUBLE-EDGED SWORD

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nal *Neurology*, studies have examined the ability of those with mild to moderate Alzheimer's to make decisions about enrolling in a clinical trial or treating a hypothetical medical condition, but not their ability to decide their dementia treatment.

To bridge that gap, Karlawish and his coauthors conducted a study that would gauge the ability of patients with mild to moderate AD to decide how to treat it. They hoped to identify characteristics that would distinguish between those capable of making such decisions and those not. Noting that many people with Alzheimer's lack awareness of their illness, they asked whether patients' insight into their diagnosis, prognosis, and symptoms would predict their ability to accept or decline a treatment.

In addition, the study explored the relationship between overall cognition and decision-making abilities. Given the widespread use of the Mini-Mental State Exam (MMSE) in dementia treatment settings, the Karlawish team wondered how traditional MMSE cut-points for dementia stages relate to decision-making competency.

Study details

Study participants, recruited from the University of Pennsylvania's Alzheimer's Disease Center, included 48 patients who met established criteria for "probable" or "possible" AD and who scored over 11 on the MMSE, indicating the presence of mild to moderate dementia. The sample also included 102 caregivers who were making decisions for or with someone with AD.

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Jason Karlawish, M.D.

The decision-making scenario involved a hypothetical medicine that slows the progression of dementia and memory loss. Both patients and caregivers heard an interviewer read a description of the medicine, including its benefits and risks, from a written page that they could later refer to while answering questions about their decision-making abilities.

To evaluate those abilities, the study used a modified version of the MacArthur Competency Assessment Tool for Treatment (MacCAT-T). The MacCAT-T measures the ability to understand a treatment's general purpose, benefits, and risks; to appreciate how those benefits and risks apply to the patient; to reason through the personal pros and cons of taking or not taking the treatment; and to make a decision about starting the treatment. The caregiver questions asked about making the decision for the patient.

A research assistant scored subjects' performance on the decision-making items. Since appreciation of the treatment's benefits correlated poorly with appreciation of the risks, the study treated the benefit and risk items as separate measures. Only 15% of patients could fully appreciate the benefits, compared to 40% for the risks.

Not surprisingly, on all tests of decision-making ability, patients performed worse than caregivers. Patients' scores ranged widely, but most caregivers did quite well.

The insight measure consisted of an open-ended health question plus three "yes" or "no" questions posed by the interviewer. One asked, "Do you have problems with your memory or thinking?" Another went, "Will your memory or thinking problems get worse?" and a third probed, "Do you have dementia or AD — even a little bit of AD or dementia?" Over half (53%) of the patients affirmed problems with memory or thinking, 34% said those problems would worsen and 53% admitted having dementia or AD.

Results

The study found that 29% of patients had very mild dementia, 31% had mild dementia, and 40% had moderate dementia. MMSE scores alone failed to identify patients who had, or lacked, each type of insight.

As noted in an editorial accompanying the article, caregiver MMSE scores ranged from 21 to 30. Since scores of 20 to 23 signify mild dementia, this finding

cautions against presuming caregivers to be dementia-free.

Three psychiatrists, experienced in competency assessment and blind to patients' scores, listened to the audiotaped interviews and independently assessed patients' capacity to decide whether to take the treatment. These experts, who showed moderate inter-rater agreement, concurred in finding 40% of the patients competent.

Scores on measures of reasoning, understanding, appreciating the benefits, and appreciating the risks showed reasonable specificity and sensitivity for determining competency, but reasoning performance best separated the competent patients from the rest. A cut-point of 7 on the 10-point reasoning scale maximized sensitivity, at 93%, and specificity, at 63%.

Patients with insight into their memory and thinking problems, as well as those with insight into their prognosis, scored significantly higher on reasoning and appreciating the medicine's benefits than those without. Patients who expressed awareness of their diagnosis performed better on reasoning, understanding, and appreciation of benefits. Those deemed competent were more likely to show all three types of insight.

Three logistic regression models examined the links between insight and competency, while controlling for overall cognition. "Insight was independently associated with preservation of capacity" and did not seem to be standing in for illness severity, Karlawish said.

Specifically, patients with insight into their memory problems were more likely to be judged competent, as were those with insight into their diagnosis. For prognosis-related insight, only a trend emerged.

Insight linked to decision-making ability

Overall, these findings underscore the relevance of patients' awareness of their disability to their continued ability to make treatment decisions in the face of mild to moderate AD. As Karlawish explained, "Even in people who had moderate-stage Alzheimer's disease, insight was associated with retaining the ability to make the decision."

In looking at the MMSE's sensitivity and specificity, the study found that scores under 19 were unlikely to mislabel many competent persons as incompetent, and scores over 22 would be unlikely to mistake many incompetent ones for competent. Karlawish and colleagues wrote that scores in between represent a "gray zone" and may warrant a closer look at patients' decision-making abilities.

These cut-points correspond to those used in dementia staging. Scores of 24 or more denote very mild-stage AD; scores of 18 or less reflect moderate-stage illness. As people go from mild to moderate AD, Karlawish said, they "start to lose the ability to make decisions about taking treatments for themselves."

Even so, using the MMSE to gauge competency can mislead, since some patients whose scores indicated moderate AD retained decision-making abilities. Consequently, Karlawish recommends that clinicians ask questions like those in the MacArthur instrument. This approach may also help caregivers, who often need to know whether they or their relative should make a particular decision.

As Karlawish said, "These are high-octane decisions, and no one instrument solves them or makes them easy," but tools such as those he and his colleagues used can "give some structure to what otherwise can become extremely emotional" situations. ■

Grisso T, Appelbaum PS: The MacArthur Competence Assessment Tool-Treatment. Sarasota, FL: Professional Resources Press, 1998.

Karlawish JHT, Casarett DJ, James BD, et al: The ability of persons with Alzheimer disease (AD) to make a decision about taking an AD treatment. *Neurology* 2005; 64(9):1514-1519. (For the measure of decision-making abilities, see the Data Supplement for the article at www.neurology.org).

McQuillen MP, Tariot P: Who can say yes (or no) to a physician — and how does the physician know they can? *Neurology* 2005; 64(9):1494-1495.

BENZODIAZEPINES

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atrists and other therapists become further educated in the risks of long-term benzodiazepine use, management of benzodiazepine withdrawal, non-drug treatments, and ways in which benzodiazepine dependence can be prevented.

While the controversy over long-term benzodiazepines use continues, patients who opt for benzodiazepine discontinuation can benefit from slow and gradual dosage tapering, combined with psychological support. Although Ashton recommends that benzodiazepine dependence can be prevented by adherence to recommendations for short-term use, she suggests[1] that the potential trauma of withdrawal can be avoided.

Some physicians, however, do prescribe benzodiazepines long-term for patients for whom discontinuation would be especially distressing, when benzodiazepine dependence is extremely high, or if repeated attempts to discontinue the drug result in rebound anxiety.

Still, Ashton cites evidence based on clinical trials, that benzodiazepines are "inappropriately prescribed" for a number of patients, particularly those with physical and psychiatric problems, the elderly living in nursing homes and those with alcohol and substance abuse.

About benzodiazepines

Benzodiazepines exert five major therapeutic actions — hypnotic, anxiolytic, anticonvulsant, myorelaxant or amnesic. Among the large number of benzodiazepines that are available, there are substantial differences in potency, and equivalent doses may vary as much as 20-fold.

There is also considerable variation in the rates at which individuals metabolize benzodiazepines and eliminate them from the body. Because of altered pharmacokinetics and pharmacodynamics, elderly persons are more sensitive to potential side effects of benzodiazepines. A number of studies have shown that alterations occur in the way these agents are distributed and eliminated in geriatric patients, and that some benzodiazepines with longer half-lives (e.g., flurazepam, diazepam, chlordiazepoxide) are more likely to cause prolonged sedation and accumulate in the body.

Adverse reactions may also be more common in the elderly and occur more frequently with advancing age. A therapeutic dose in a 65-70 year old patient may produce significant side effects in patients 75 years of age or older.

Benzodiazepines can cause sedation, ataxia, psychomotor impairment and, according to some studies, cognitive impairment.[2] Although opinion remains divided, reflecting a variety of confounds between contradictory data, the risk/benefit ratio needs to be assessed by the clinician, and patients being considered for long-term benzodiazepine treatment

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