

AD8 Tool Touted for Annual Cognitive Screening

BY MICHELE G. SULLIVAN

The Affordable Care Act, which became law this January, stipulates that clinicians must assess patients aged 65 years or older for cognitive impairment as part of their annual wellness visit.

But the U.S. Preventive Services Task Force has never endorsed a screening tool for cognitive decline, noting that no

data consistently support one of the many existing tools over another.

So, what's a busy primary care physician to do? Some researchers – including Dr. James Galvin of Washington University, St. Louis – think a screening tool called the AD8 could be one answer.

Dr. Galvin created the screening tool along with colleagues at the university's Alzheimer's Disease Research Center. During a Webinar sponsored by the

Alzheimer Research Forum, he presented data showing that AD8 is fast, easy, inexpensive, and very accurate in identifying patients who are beginning to show early signs of cognitive decline.

In an unselected population, the tool has a sensitivity of more than 84% and specificity of more than 80%, although both measures were much higher in the dementia clinic where it was piloted. Overall, the AD8 has proved more use-

ful than the Mini Mental State Examination in picking out patients with the very earliest signs of cognitive impairment, Dr. Galvin said during the Webinar (*Arch. Neurol.* 2007;64:718-24).

The eight-question survey asks an informant whether the patient has experienced any changes in executive function or memory over the past few years.

"It's brief, inexpensive, easy to give and score, reliable, socially acceptable, and

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culturally sensitive," Dr. Galvin said.

Because it provides a picture of change related to baseline, the AD8 avoids the problem of a "snapshot" test, which could, for example, falsely identify cognitive problems in someone who has never had a good memory. Because the AD8 does not test patients on acquired learning, it is not educationally biased. The test also is culturally neutral because it focuses on changes in basic activities in which everyone engages.

Most screening tests "share performance-based problems," he said. "They might be insensitive to very early dementia, have a cultural or educational bias, or be heavily weighted toward memory impairment or another single cognitive domain. And unless they are done serially, you really have no idea where the patient was before [the test], and no sense of whether the findings interfere with their occupation or social function."

The AD8 asks informants to answer yes, no, or don't know to whether the patient has changed in eight areas: problems with daily judgment and decision making; decreased interest in hobbies or activities; repeating things over and over; trouble learning how to use a new tool or appliance; forgetting the month or year; trouble with financial affairs; trouble recalling appointments; and daily problems with thinking and memory.

A score of two or more "yes" answers is a positive screen, indicating that cognitive impairment is likely. Positive screening results also strongly correlate with the new Alzheimer's disease biomarker diagnostic standards.

Patients with a positive AD8 are significantly more likely to have brain atrophy in the temporal lobe, hippocampus, and parahippocampal gyrus than are those with a negative screen. Patients with a positive screen also are more likely to have beta amyloid₄₂ brain plaques, to have decreased beta amyloid₄₂, increased tau, and abnormal beta amyloid/tau ratios in cerebrospinal fluid (*Brain* 2010;133:3290-300).

However, the test is not a method of diagnosing any particular cognitive dis-

Continued on following page

Silenor®

(doxepin) tablets for oral administration

Brief summary of Prescribing Information. For complete Prescribing Information, consult official package insert.

INDICATIONS AND USAGE

Silenor is indicated for the treatment of insomnia characterized by difficulty with sleep maintenance. The clinical trials performed in support of efficacy were up to 3 months in duration.

CONTRAINDICATIONS

Hypersensitivity:

Silenor is contraindicated in individuals who have shown hypersensitivity to doxepin HCl, any of its inactive ingredients, or other dibenzoxepines.

Co-administration With Monoamine Oxidase Inhibitors (MAOIs):

Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Do not administer Silenor if patient is currently on MAOIs or has used MAOIs within the past two weeks. The exact length of time may vary depending on the particular MAOI dosage and duration of treatment.

Glaucoma and Urinary Retention:

Silenor is contraindicated in individuals with untreated narrow angle glaucoma or severe urinary retention.

WARNINGS AND PRECAUTIONS

Need to Evaluate for Comorbid Diagnoses:

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Exacerbation of insomnia or the emergence of new cognitive or behavioral abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with hypnotic drugs.

Abnormal Thinking and Behavioral Changes:

Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a hypnotic, with amnesia for the event) have been reported with hypnotics. These events can occur in hypnotic-naïve as well as in hypnotic-experienced persons. Although behaviors such as "sleep-driving" may occur with hypnotics alone at therapeutic doses, the use of alcohol and other CNS depressants with hypnotics appears to increase the risk of such behaviors, as does the use of hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Silenor should be strongly considered for patients who report a "sleep-driving" episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a hypnotic. As with "sleep-driving", patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably.

Suicide Risk and Worsening of Depression:

In primarily depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), has been reported in association with the use of hypnotics. Doxepin, the active ingredient in Silenor, is an antidepressant at doses 10- to 100-fold higher than in Silenor. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Risk from the lower dose of doxepin in Silenor cannot be excluded. It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

CNS Depressant Effects:

After taking Silenor, patients should confine their activities to those necessary to prepare for bed. Patients should avoid engaging in hazardous activities, such as operating a motor vehicle or heavy machinery, at night after taking Silenor, and should be cautioned about potential impairment in the performance of such activities that may occur the day following ingestion. When taken with Silenor, the sedative effects of alcoholic beverages, sedating antihistamines, and other CNS depressants may be potentiated. Patients should not consume alcohol with Silenor. Patients should be cautioned about potential additive effects of Silenor used in combination with CNS depressants or sedating antihistamines.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of labeling:

- Abnormal thinking and behavioral changes.
- Suicide risk and worsening of depression.
- CNS Depressant effects.

Clinical Trials Experience:

The pre-marketing development program for Silenor included doxepin HCl exposures in 1017 subjects (580 insomnia patients and 437 healthy subjects) from 12 studies conducted in the United States. 863 of these subjects (580 insomnia patients

and 283 healthy subjects) participated in six randomized, placebo-controlled efficacy studies with Silenor doses of 1 mg, 3 mg, and 6 mg for up to 3-months in duration. Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. However, data from the Silenor studies provide the physician with a basis for estimating the relative contributions of drug and non-drug factors to adverse reaction incidence rates in the populations studied.

Associated with Discontinuation of Treatment:

The percentage of subjects discontinuing Phase 1, 2, and 3 trials for an adverse reaction was 0.6% in the placebo group compared to 0.4%, 1.0%, and 0.7% in the Silenor 1 mg, 3 mg, and 6 mg groups, respectively. No reaction that resulted in discontinuation occurred at a rate greater than 0.5%.

Adverse Reactions Observed at an Incidence of ≥2% in Controlled Trials:

Table 1 shows the incidence of treatment-emergent adverse reactions from three long-term (29 to 85 days) placebo-controlled studies of Silenor in adult (N=221) and elderly (N=494) subjects with chronic insomnia. Reactions reported by investigators were classified using a modified MedDRA dictionary of preferred terms for the purposes of establishing incidence. The table includes only reactions that occurred in 2% or more of subjects who received Silenor 3 mg or 6 mg in which the incidence in subjects treated with Silenor was greater than the incidence in placebo-treated subjects.

Incidence (%) of Treatment-Emergent Adverse Reactions in Long-term Placebo-Controlled Clinical Trials

System Organ Class Preferred Term ^a	Placebo (N=278)	Silenor 3 mg (N=157)	Silenor 6 mg (N=203)
Nervous System Disorders			
Somnolence/Sedation	4	6	9
Infections and Infestations			
Upper Respiratory Tract Infection/Nasopharyngitis	2	4	2
Gastroenteritis	0	2	0
Gastrointestinal Disorders			
Nausea	1	2	2
Vascular Disorders			
Hypertension	0	3	<1

^aIncludes reactions that occurred at a rate of ≥2% in any Silenor-treated group and at a higher rate than placebo.

The most common treatment-emergent adverse reaction in the placebo and each of the Silenor dose groups was somnolence/sedation.

Studies Pertinent to Safety Concerns for Sleep-promoting Drugs:

Residual Pharmacological Effect in Insomnia Trials:

Five randomized, placebo-controlled studies in adults and the elderly assessed next-day psychomotor function within 1 hour of awakening utilizing the digit-symbol substitution test (DSST), symbol copying test (SCT), and visual analog scale (VAS) for sleepiness, following night time administration of Silenor. In a one-night, double-blind study conducted in 565 healthy adult subjects experiencing transient insomnia, Silenor 6 mg showed modest negative changes in SCT and VAS. In a 35-day, double-blind, placebo-controlled, parallel group study of Silenor 3 and 6 mg in 221 adults with chronic insomnia, small decreases in the DSST and SCT occurred in the 6 mg group. In a 3-month, double-blind, placebo-controlled, parallel group study in 240 elderly subjects with chronic insomnia, Silenor 1 mg and 3 mg was comparable to placebo on DSST, SCT, and VAS.

DRUG INTERACTIONS

Cytochrome P450 Isozymes:

Silenor is primarily metabolized by hepatic cytochrome P450 isozymes CYP2C19 and CYP2D6, and to a lesser extent, by CYP1A2 and CYP2C9. Inhibitors of these isozymes may increase the exposure of doxepin. Silenor is not an inhibitor of any CYP isozymes at therapeutically relevant concentrations. The ability of Silenor to induce CYP isozymes is not known.

Cimetidine:

Silenor exposure is doubled with concomitant administration of cimetidine, a nonspecific inhibitor of CYP isozymes. A maximum dose of 3 mg is recommended in adults and elderly when cimetidine is co-administered with Silenor.

Alcohol:

When taken with Silenor, the sedative effects of alcohol may be potentiated.

CNS Depressants and Sedating Antihistamines:

When taken with Silenor, the sedative effects of sedating antihistamines and CNS depressants may be potentiated.

Tolazamide:

A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 g/day) 11 days after the addition of oral doxepin (75 mg/day).

USE IN SPECIFIC POPULATIONS

Pregnancy:

Pregnancy Category C:

There are no adequate and well-controlled studies of Silenor in pregnant women. Silenor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Administration of doxepin to pregnant animals resulted in adverse effects on offspring development at doses greater than the maximum recommended human dose (MRHD) of 6 mg/day. When doxepin (30, 100, and 150 mg/kg/day) was administered orally to pregnant rats during the period of organogenesis, developmental toxicity (increased incidences of fetal structural abnormalities and decreased fetal body weights) was noted at ≥100 mg/kg/day. The plasma exposures (AUC) at the no-effect dose for embryo-fetal developmental toxicity in rats (30 mg/kg/day) are approximately 6 and 3 times the plasma AUCs for doxepin and nordoxepin (the primary metabolite in humans), respectively, at the MRHD. When administered orally to pregnant rabbits (10, 30, and 60 mg/kg/day) during the period of organogenesis, fetal body weights were reduced at the highest dose in the absence of maternal toxicity. The plasma exposures (AUC) at the no-effect dose for developmental effects (30 mg/kg/day) are approximately 6 and 18 times the plasma AUCs for doxepin and nordoxepin, respectively, at the MRHD. Oral administration of doxepin (10, 30, and 100 mg/kg/day) to rats throughout the pregnancy and lactation periods resulted in decreased pup survival and transient growth delay at the highest dose. The plasma exposures (AUC) at the no-effect dose for adverse effects on pre- and postnatal development in rats (30 mg/kg/day) are approximately 3 and 2 times the plasma AUCs for doxepin and nordoxepin, respectively, at the MRHD.

Labor and Delivery:

The effects of Silenor on labor and delivery in pregnant women are unknown.

Nursing Mothers:

Doxepin is excreted in human milk after oral administration. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking the higher dose of doxepin used to treat depression. Caution should be exercised when Silenor is administered to nursing women.

Pediatric Use:

The safety and effectiveness of Silenor in pediatric patients have not been evaluated.

Geriatric Use:

A total of 362 subjects who were ≥65 years and 86 subjects who were ≥75 years received Silenor in controlled clinical studies. No overall differences in safety or effectiveness were observed between these subjects and younger adult subjects. Greater sensitivity of some older individuals cannot be ruled out. Sleep-promoting drugs may cause confusion and over-sedation in the elderly. A starting dose of 3 mg is recommended in this population and evaluation prior to considering dose escalation is recommended.

Use in Patients With Hepatic Impairment:

Patients with hepatic impairment may display higher doxepin concentrations than healthy individuals. Initiate Silenor treatment with 3 mg in patients with hepatic impairment and monitor closely for adverse daytime effects.

Use in Patients With Sleep Apnea:

Silenor has not been studied in patients with obstructive sleep apnea. Since hypnotics have the capacity to depress respiratory drive, precautions should be taken if Silenor is prescribed to patients with compromised respiratory function. In patients with severe sleep apnea, Silenor is ordinarily not recommended for use.

OVERDOSAGE

Doxepin is routinely administered for indications other than insomnia at doses 10- to 50-fold higher than the highest recommended dose of Silenor.

The signs and symptoms associated with doxepin use at doses several-fold higher than the maximum recommended dose (Excessive dose) of Silenor for the treatment of insomnia are described, as are signs and symptoms associated with higher multiples of the maximum recommended dose in the full prescribing information.

PATIENT COUNSELING INFORMATION

Prescribers or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with hypnotics, should counsel them in appropriate use, and should instruct them to read the Medication Guide.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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Continued from previous page

order – even mild cognitive impairment, Dr. Galvin said. A positive AD8 will most likely mean additional tests for the patient, including brain imaging, biomarkers, neuropsychological testing, and other diagnostic activities.

Validation studies of the AD8 have confirmed that it can identify early changes in a plethora of dementias, including Alzheimer's disease and progressive aphasia, as well as Lewy body, frontotemporal, and vascular dementia. Therefore, early identification is its biggest advantage, he said.

"As new disease-modifying medications are developed, those at the earliest stages of their disease will probably get the biggest benefit," Dr. Galvin said. An earlier diagnosis not only affords the opportunity to benefit from new drugs, when they become available, but also allows families and patients to work together to plan the future, while the patient is still able to make meaningful contributions.

AD8's future is by no means ensured. The tool is available online, free to any clinician who wants to download it. But whether primary care doctors will use it – and whether patients will want it – is another matter, said Dr. Galvin and Dr. Tracey Holsinger of Duke University and the Durham (N.C.) Veterans Affairs Medical Center.

Conflicting directives from the federal government and the USPSTF might make clinicians cringe when faced with the cognitive-screening mandate, Dr. Galvin said. "There is just no clear plan about how best to screen and what instrument to use. ... Dementia screening simply has not been a routine part of primary care practice," and certainly not for a nontargeted population that begins at a relatively low-risk age for age-related dementias. "Targeted screening makes a lot more sense, and it's my belief that large population screening will yield very few cases." However, he said, this is the hand that politicians have dealt primary care, "unless the Task Force can be persuaded to review its recommendations and make new ones based on the current data."

Even if physicians quail at the thought of having one more box to tick off in an annual exam, patients will

probably like the security an annual cognitive screen can provide, Dr. Holsinger said. She and her colleagues recently conducted a survey of 345 primary care patients at the Durham VA Medical Center. After discussing the risks and benefits of a cognitive screen that could identify early dementia, the subjects were asked whether they would want to know of their probable diagnosis. "Eighty-one percent said they would want to know," she said.

Factors associated with the desire for screening were acceptance of other screening tests (depression, breast, and prostate cancer; odds ratio 3.7), male gender (OR 3.2), and the belief that effective treatment for dementia exists (OR 2) (Int. J. Geriatr. Psych. 2010 [doi:10.1002/gps.2536]).

The AD8 sounds good on the surface, but how it will fit into a busy primary care day is still unclear, said Dr. Eric Tan-

galos, an internist at the Mayo Clinic, Rochester, Minn. Having an informant fill out the paper might throw some bias into the pot at the very beginning of the process, he said during the webinar. "In my practice, if a 65-year-old shows up for an annual wellness exam with a spouse, that sends my red flags flying. We

need to be very cautious about applying an instrument [that was tested in dementia clinics] to a broad population that is not at a high-risk age."

Primary care physicians already are ultracautious about entering the dementia arena, he said. "We already know primary care docs do not want to open Pandora's box, even when the disease is confronting them. We're saying 'Run toward that diagnosis, rather than run away from it.'"

Dr. Galvin agreed, but reminded the panel that the die has been cast. "There is not a lot of evidence that anyone needs to be seen annually for something like this – this is really a political approach to health care that is quite a bit different from anything the USPSTF policy has recommended. But even though we're not exactly sure how it will all play out, it's going to be up to the practices to get it done."

None of the panel members expressed any financial conflicts related to the screening tool. ■

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