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Trial to Test ECT for Severe Agitation in Alzheimer's

By Pauline Anderson

ATLANTA — With funding for a new trial secured, electroconvulsive therapy (ECT) is gaining ground as a possible treatment for severe agitation and aggression in patients with Alzheimer's disease (AD).

"New treatments for severe agitation in AD refractory to standard interventions are timely and warranted," **Brent P. Forester, MD**, chief, **Division of Geriatric Psychiatry**, **McLean Hospital**, and associate professor of psychiatry, Harvard Medical School, told Medscape Medical News.

For years, Forester and his colleagues have been gathering data on the use of ECT to treat severe agitation in patients with dementia and are now set to test the intervention in a randomized controlled trial.

The findings from earlier pilot studies and the study design for this randomized controlled trial were presented here at American Association for Geriatric Psychiatry (AAGP) 2019 Annual Meeting.

No Approved Medications

Agitation and other neuropsychiatric symptoms such as apathy occur in over 90% of AD patients. Such symptoms increase morbidity and mortality among patients and contribute to caregiver burden.

There are no FDA-approved drug treatments for severe agitation in AD. Psychotropic medications, especially antipsychotics, are widely used off-label, but they have limited efficacy and there are safety concerns.

Behavioral therapies, which are recommended as first-line treatments, require substantial time to take effect and may be relatively ineffective for the most severely agitated patients.

ECT is a well-validated and FDA-approved treatment for major depression, the depression phase of bipolar disorder, and catatonia.

During an ECT procedure, an electrical stimulation is delivered to the brain which causes a seizure. For reasons not completely understood, this appears to change patterns of blood flow, brain chemistry, and metabolism in certain areas of the brain and have an impact on behavior.

Some patients may experience temporary confusion, memory loss, headache, and discomfort after an ECT treatment.

Forester said he first became interested in ECT as a possible treatment for dementia patients about 17 years ago when he came across a hospitalized woman in her 60s with AD who was nonverbal and displayed severe aggression. Behavioral modification therapy and medications were ineffective.

"She was attacking other residents and staff members," said Forester.

A colleague suggested trying ECT. But Forester was concerned about exacerbating cognitive dysfunction in an already cognitively impaired patient.

In the end, ECT was used on this patient as a last resort.

"After the third treatment, she started to smile, and was no longer physically aggressive; after the eighth treatment, she went home. We had no idea if this would be helpful, but it was dramatically helpful," said Forester.

Five-Year Study

Since then, Forester and his team have been collecting and publishing data on individual dementia patients with agitation and aggression who received this intervention.

In addition, a multisite, prospective case series investigating ECT in 23 consecutive dementia inpatients showed it significantly reduced agitation in these treatment-resistant patients.

Furthermore, results of a retrospective chart review study of 16 AD patients who underwent ECT for agitation showed only two experienced more than transient confusion post-ECT that required treatment and no other clinically significant adverse events were noted.

Despite, these promising findings, the investigators were unable to obtain funding for a randomized controlled trial. "It's been a labor of love without funding for a decade and a half," said Forester.

That has now changed. Funding from the National Institute of Aging has been secured for a 5-year study to determine the safety and efficacy of ECT.

The study will include five sites across the United States and 200 patients with moderate to severe AD with severe, treatment-resistant agitation.

Forester will be a co-principal investigator along with Georgios Petrides, MD, who heads the division of ECT at the Zucker Hillside Hospital of Northwell Health in New York.

The single-blind study will have two arms. Patients in the intervention group will receive ultra-brief pulse right unilateral ECT treatments.

"This method of ECT has been shown to be safer in terms of cognitive side effects," said Forester.

Not Sham ECT

Patients will receive the treatment three times a week for three weeks. However, the number of ECT sessions may change depending on patient response.

"We don't want to over-treat them. They will be treated until they are well enough to leave the hospital or symptoms are reduced," said Forester.

The control group will receive what the investigators are calling "simulated ECT." As with the real ECT group, controls will be taken to the ECT suite, have an IV set up for medications and fluids as needed, and have the gel administered to their scalp but they will not receive anesthesia.

"Our goal is to blind the inpatient treatment team while allowing for one-to-one supervised care of the patients who are

taken to the ECT suite but not treated. In the old days, we did sham ECT. This is not sham; it's not anesthesia without treatment," said Forester.

Both groups will receive usual care, which will involve environment modifications, behavioral interventions, and pharmacotherapy.

The primary efficacy outcome measure will be the Cohen Mansfield Agitation Inventory (CMAI). Secondary outcomes will include the Neuropsychiatric Inventory-Clinician Version (NPI-C), Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Scale (ADCS-CGIC), and Pittsburgh Agitation Scale (PAS).

Safety and tolerability will be assessed with the Severe Impairment Battery-8 item (SIB-8), the Confusion Assessment Method (CAM), and adverse event monitoring.

The investigators will collect outcomes of safety and efficacy at the end of three, six, and nine treatments, and then unblind the treatment team. After the inpatient phase, participants will be followed at months 1,3, 6, and 12 to collect clinical and safety data as well as data on utilization of healthcare services.

Filling a Treatment Gap

agitation in AD and fill a gap that currently exists in clinical practice.

"Clinicians treating individuals suffering from Alzheimer's dementia complicated by severe agitation or aggression often face limited therapeutic options due to modest efficacy and considerable safety concerns of available treatments," he said.

Forester noted that ECT is not being studied not for mild to moderate behavioral symptoms of dementia but for severe symptoms of agitation and aggression that have not responded to standard environmental, behavioral and medication interventions.

ECT has been around since the 1930s. But until improved anesthetics and muscle relaxants became available, some patients had complications from the seizures, including falls and fractures.

With today's technology, though, that doesn't happen, said Forester. "The patients have a seizure but no motor movements, and it's remarkably safe."

Although some celebrities have told their personal stories of how ECT has helped them, the treatment remains somewhat controversial. There's still stigma surrounding its use, and the negative portrayal of a psychiatric hospital and ECT in the movie One Flew Over the Cuckoo's Nest "didn't help," said Forester.

Compelling Argument

Commenting on the research for Medscape Medical News, Prasad Padala, MD, professor of psychiatry and geriatrics, University of Arkansas for Medical Sciences, said it has "a lot of potential."

The authors make "a compelling argument" for use of ECT in dementia patients with agitation, which is "a huge problem," said Padala "The team is really well poised to come up with a breakthrough treatment for it. It's very exciting."

The new study "go a long way toward" providing solid evidence that ECT works for agitation in dementia patients, he said

He noted that the researchers have "really thought through" how to minimize transient memory problems that can

accompany the procedure.

Padala noted that ECT is "the best treatment option we know of" for major depression. "When you look at effect sizes of response for major depression, ECT has the best track record."

Some psychiatrists, however, delay prescribing ECT in depressed patients until they have failed several trials of medication.

"It's much easier to prescribe a medication than ECT, although it is pretty accessible. ECT should be done sooner in certain populations than what we are doing currently," said Padala.

The investigators and Padala have disclosed no relevant financial relationships.

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