Antihypertensive's Antidepressant Effects Explored

BY BRUCE JANCIN
Denver Bureau

VIENNA — Mecamylamine, an old, rarely prescribed, truly obscure antihypertensive agent, may be favorably reincarnated as an antidepressant with a completely novel mechanism of action—and vastly greater potential use.

The drug displayed favorable safety and efficacy as augmentation therapy in a double-blind, placebo-controlled trial in patients with major depressive disorder who were nonresponders to citalopram (Celexa) monotherapy, Dr. Geoffrey C. Dunbar reported at the annual congress of the European College of Neuropsychopharmacology.

"This study provides the first substantive clinical evidence that compounds where the primary pharmacology is antagonism to neuronal nicotinic receptors will have antidepressant properties," said Dr. Dunbar, vice president for clinical development and regulatory affairs at Targacept Inc., Winston-Salem, N.C.

The mechanism of benefit is the blocking of the central nervous system (CNS) nicotinic receptors, which is thought to restore balance to a deranged cholinergic tone implicated in depression.

"It's really very exciting, because there have been no new pharmacologic approaches in depression therapy in 30 years or more," the psychiatrist said later in an interview.

However, Targacept will move forward with development not of mecamylamine, but of its S-enantiomer, as a treatment for depression. The enantiomer, trade name Amplixa, has gotten the green light from the Food and Drug Administration for accelerated development on the strength of the reassuring safety profile established over many years by its racemic relative, mecamylamine, Dr. Dunbar continued.

Mecamylamine was approved for treatment of hypertension in the mid-1950s. It never gained broad use as an antihypertensive agent, and was prescribed mainly for hypertensive crises in paraplegics. In addition, today mecamylamine sees some off-label use for the behavioral and mood disorders associated with autism and Tourette syndrome, according to Dr. Dunbar.

Mecamylamine is a broad-spectrum nicotinic receptor antagonist, meaning that it blocks receptors located in the periphery of, as well as those in, the CNS. An insight that was key to unlocking its antidepressant potential was the discovery that at dosages of 2.5-10 mg/day—one-tenth of the dosages used in hypertension—the drug antagonizes CNS neuronal nicotinic receptors with no effect on those in the periphery—and no impact on blood pressure.

'There have been no new pharmacologic approaches in depression therapy in 30 years or more.'

DR. DUNBAR

Dr. Dunbar presented a nine-center clinical trial conducted in the United States and India involving 450 patients with major depressive disorder who were placed on 6 weeks of open-label citalopram titrated from 20 to 40 mg/day. The 192 patients deemed suboptimal responders based on a 17-item Hamilton Depression Rating Scale (HAMD) score of 14 or more and a Clinician Global Impression Severity of Illness score of at least 4 entered the double-blind phase, in which they were randomized to mecamylamine at 5-10 mg/day or placebo for 8 weeks while continuing on citalopram.

From a mean HAMD of 20.5 at the start of the double-blind phase, the mecamylamine group experienced a 12.3-point decline, 2 points more than in the placebo arm. The mecamylamine group also demonstrated a mean 3.3-point greater decline, compared with placebo, on the Montgomery-Asberg Depression Rating Scale and a 0.37-point greater improvement on the Clinician Global Impression of Severity of Illness, both of which were significant differences.

In addition, patients on mecamylamine experienced a nearly threefold greater drop in Sheehan Irritability Scale scores than those on placebo. "This may be a particularly beneficial effect. Irritability is not a symptom that you typically think of in conjunction with depression. However, it is common in depressed patients." ■