# Genotype May Dictate Response to Sibutramine

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BOSTON — Weight loss in an overweight or obese person taking sibutramine may be governed by whether the individual has a particular genotype related to the regulation of endogenous serotonin reuptake, Ms. Maria Vazquez Roque proposed at a meeting on neurogastroenterology and motility.

Sibutramine, a noradrenergic and serotonergic reuptake inhibitor, is one of two FDA-approved medications for the long-term treatment of obesity. One drawback to its use is the wide variability in response to the drug among various individuals. Investigators such as Ms. Vazquez Roque are now applying pharmacogenomics to unravel the genetic underpinnings of the differences in individuals' reactions to, or metabolism of, drugs affecting the GI system.

In her study, Ms. Vazquez Roque, who is a master's degree candidate in clinical research at Mayo Graduate School in Rochester, Minn., and her colleagues randomly assigned 24 overweight and 24 obese individuals (as determined by body mass index) to receive sibutramine (15 mg/day) or placebo for 12 weeks.

The investigators conducted DNA analyses of blood samples from the patients to determine whether the patients' responses to sibutramine correlated with the polymorphisms of a number of candidate genes related to serotonin and norepinephrine. These included SERT-P (also known as SLC6A4), the promoter region of the serotonin transporter protein; á-2 MspI, a promoter for the á-2A adrenergic receptor; phenylethanolamine-N-methyl transferase (PNMT), the enzyme that converts norepinephrine to epinephrine; and GN3 C825T, which modulates ligand-receptor interactions.

Only one genotype could be correlated with a differential response to sibutramine. Patients with the SERT-P LS/SS (heterozygous/short) genotype lost an average of 6.1 kg (plus or minus 1.0 kg), significantly more than the 0.1 kg (plus or minus 0.9 kg) weight gain of the placebo group.

Patients who were homozygous for the SERT-P LL (long) genotype showed moderate weight loss with sibutramine that was comparable with the weight loss observed with placebo. No other candidate gene showed a variable response to sibutramine.

"It is conceivable that having the LS/SS genotype enhances the effect of sibutramine, leading to greater inhibition of serotonin reuptake, leading to higher concentration of serotonin at the synapse, and greater ligand/receptor interaction in hypothalamic nuclei," said Ms. Vazquez Roque. The ventromedial and paraventricular nuclei of the hypothalamus are thought to have a role in central appetite regulation.

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**DR. CAMILLERI**

"The data are preliminary, but if confirmed, they could point to a way of selecting patients who are more likely to respond to sibutramine," said Dr. Michael Camilleri, professor of medicine and physiology at Mayo Medical School, Rochester, Minn., and a coauthor of the abstract.

In a separate presentation, Dr. Camilleri reviewed other examples of genetic influences on the response to drugs that affect the GI system, as well as GI symptomatology. For instance, patients with homozygous polymorphism of SERT show an enhanced response to alosetron, a 5HT-3 antagonist that is used in women with severe, diarrhea-predominant IBS (Gastroenterology 2002;123:425-32). Dr. Camilleri recently found that the CC genotype of GN3 is also associated with a predisposition to developing meal-unrelated dyspepsia (Am. J. Gastroenterol. 2006;101:581-92).

Last year, the Food and Drug Administration approved a DNA chip–based test, the AmpliChip CYP450 (Roche Diagnostics), which helps physicians establish a patient's genotype regarding 2D6 and 2C19 polymorphisms before initiating therapy. "It is now possible to understand the underlying genetic status of your patient and perhaps individualize dose or select a drug based on underlying genotype. We are moving more toward individualized medicine," Dr. Camilleri said. ■