# Post-marketing studies finding adverse events in drugs used in children

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The Food and Drug Administration Modernization Act (FDAMA, 1997), designed to stimulate more drug safety studies in children, has resulted in more than 130 label changes since its inception nearly six years ago, according to researchers at Duke Children's Hospital. Their analysis appears in the September issue of *Pediatrics*.

Under this and subsequent renewal of this legislation, pharmaceutical companies were given a six-month extension of their exclusive marketing rights on a drug if they performed clinical trials requested by the FDA to determine the drugs' safety, dosing, and efficacy in children.

According to P. Brian Smith, MD, an assistant professor in Duke's department of pediatrics, many safety concerns cannot be detected until after the introduction of a product to a larger and more diverse population. The Best Pharmaceuticals for Children Act (2002) required the FDA to review and report to a public expert panel the adverse events occurring after granting pediatric exclusivity. That effort was needed because pediatric clinical trials are notoriously small, making it more likely that some safety concerns would not be detected until after the drug is used in a larger pediatric population.

Using MedWatch, the FDA's computerized information database for collecting reports of adverse events, the FDA's Pediatric Advisory Committee reviewed 67 drugs granted the extension. "This is a voluntary, cost-effective reporting system that can identify adverse events that may never have been seen in a clinical trial," Smith said.

"Just because a drug goes through testing and clinical trials does not mean its entire safety profile is known," says Danny Benjamin, MD, a co-author of the study and pediatrician at Duke Children's Hospital. "Before this incentive, there was no systematic, focused pediatric review of the data provided to the FDA's adverse event reporting system. Now, field experts in pediatrics are evaluating the data. That's what's so unique about this effort."

The majority of the 67 drugs studied (65.7 percent) did not appear to cause enough adverse events to require continued pediatric monitoring. However, nearly one in five drugs studied required label changes consisting of additional warnings and cautions for use in children, and several of the adverse events revealed during this process were considered life threatening. Some of those labeling changes included:

-- Black Box warning and development of patient information for selective serotonin reuptake inhibitors (SSRIs) regarding potential for suicidality and neonatal toxicity/withdrawal syndrome.

-- Box warning for transdermal opioid analgesis (Duragesic) alerting that inappropriate use may result in serious adverse reactions, including death.

-- Labeling change for methylphenidate (Concerta) to address the potential for psychiatric events.

The Duke researchers say their findings support the approach that pediatric post-marketing surveillance is crucial, and that physicians, nurses, parents and others should take the job of reporting adverse effects seriously. Very rare serious adverse events are seldom defined during a study of a few hundred children and learning about these events is often dependent on the reporting of them from caretakers and parents.

"Unfortunately, few clinicians and patients know this reporting system exists," says Smith. "In the Duke Neonatal Intensive Care Unit, the pharmacist reports adverse drug events to MedWatch. But I'm not sure that happens at every hospital. A lot of physicians don't know it's available. This publication is somewhat of an advertisement that this program is available."

Smith urges parents to report adverse reactions they see. The FDA does not release any confidential information provided. Nor do the parents have to be certain that a drug exposure was the cause. It's the FDA's job to further investigate these events and any possible relationships to therapy, Smith said.

Source: Duke University