Obesity experts spotlight safety gap in clinical trials and drug labeling for people with obesity

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A new opinion piece published in *Health Affairs Forefront* raises questions around current approaches to assess drug safety and

effectiveness in people with obesity. The article sheds light on how increased body fat can modify the effects of drugs used to treat common conditions, in some cases rendering the drugs ineffective or unsafe for people with obesity.

The article, titled "Assessments Of Drug Safety And Effectiveness Continue To Fail People With Obesity," argues that drug manufacturers should be required to show correct dosing instructions on their labels for people with obesity when they are well-known, and when appropriate, include people with obesity in clinical trials during the drug approval process.

"People with obesity deserve to know that the prescription drugs they take are safe and effective for them," according to William Dietz, Director of the STOP Obesity Alliance at the Milken Institute School of Public Health at the George Washington University, and one of the paper's authors. "Today, neither patients nor their providers know how some drugs may act differently in people with obesity."

According to the article, the FDA has recognized that people with obesity are often intentionally excluded from clinical trials in an effort to reduce the observed variability of early-phase trials. For some drugs, this makes little or no clinical difference. But with drugs that are lipophilic, meaning highly fat-soluble, the difference in clinical impact for patients with obesity can be serious or even fatal.

For example, brexpiprazole, marketed under the brand name Rexulti, is a drug that treats schizophrenia and depression, two very serious conditions with life-threatening implications. Rexulti is lipophilic. It was approved by the FDA in 2015 without being tested fully on people with obesity, despite the fact that around 60% of people with schizophrenia have obesity.

A 2021 study conducted by former senior FDA officials, as well as researchers at Tufts and Emerald Lake Safety, showed that Rexulti took substantially longer to reach effective levels in people with obesity—and that in some patients it might never reach effective levels. Yet the label provides no specific instructions or warning for patients or their providers regarding how to treat people with obesity.

This lack of information may have serious consequences. For example, people with schizophrenia who are under-treated or who stop treatment may suffer mental health crises or harm themselves or others.

As another example, posaconazole, marketed under the brand name Noxafil, is a drug that treats fungal infections such as candidiasis, which is reported to be more frequent in people with obesity. Researchers at Tufts and Emerald Lake Safety showed that the half-life of posaconazole is significantly longer in people with obesity. This results in prolonged inhibition of a key drug metabolizing enzyme and puts people with obesity at risk of dangerous drug-drug interactions for weeks after they stop taking posaconazole. There is no information on the Noxafil label to address these findings, despite its known risks.

"These data are part of the growing body of literature demonstrating that obesity can change the pharmacokinetics of some drugs, including changes in metabolism, clearance, volume of distribution, and half-life," stated Christina Chow, Head of Research at Emerald Lake Safety and co-author. "Studies must be done in people with obesity to assess the drugs' clinical impact before they are on the market, and labels must reflect this information. Unfortunately, the effects of obesity on the pharmacokinetics of many commonly prescribed drugs are still unknown."

The authors recommend a three-pronged approach to address the gap:

- First, the FDA should revise its Clinical Trials Guidance Documents and Regulations Relating to Good Clinical Practice to require testing on people with obesity.
- Second, whenever appropriate, drug manufacturers should include information on the effects of obesity on specific drugs in the drug package insert.
- Third, a reporting system for adverse events relating to drug metabolism in people with obesity should be established to enable the FDA and drug manufacturers to identify and track issues.

"Regulators and policy makers can and should act now to address this gap, reduce risks to patients with obesity, and improve health," says co-author David J. Greenblatt, Louis Lasagna Endowed Professor of Immunology at Tufts University.

STOP Obesity Alliance includes a diverse group of business, consumer, government, advocacy, and health organizations dedicated to reversing the obesity epidemic in the United States. Emerald Lake Safety conducts independent research to make pharmaceuticals safer.

More information: Assessments Of Drug Safety And Effectiveness Continue To Fail People With Obesity, *Health Affairs Forefront* (2023). DOI: 10.1377/forefront.20230829.36462

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