People with obesity are not appropriately included in clinical trials for drug approval, leading to incomplete data on the safety and effectiveness of drugs in this population.

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Abstract

Obesity is associated with several comorbidities such as Type 2 Diabetes, hypertension, dyslipidemia, cancers, depression, and anxiety. Treatment of obesity and its comorbidities often require the use of prescription drugs, many of which have not been fully evaluated in people with obesity. Despite a growing body of research on this topic, the impact of obesity on the pharmacokinetics and pharmacodynamics of drugs is often under-studied by drug sponsors and regulators.

We conducted a survey of clinicaltrials.gov to assess the presence of weight- or BMI-based Inclusion/Exclusion criteria in studies of investigational drugs in 2022 as well as the scientific literature to assess whether pharmacokinetic studies have been conducted in people with obesity for a variety of commonly used drugs. We then examined whether pharmacokinetic changes were determined to be clinically relevant and if specific changes to clinical practice were recommended.

Over half of studies listed on clinicaltrials.gov in 2022 did not mention weight or BMI; when it was listed as an inclusion/exclusion criteria, it was most often used to exclude people with obesity. We also present examples in which changes to drug dosing information for patients with obesity should be made. We highlight serious gaps between what is known about the effects of obesity on drug disposition and the current use of drugs according to drug prescribing information and clinical practice.

Results

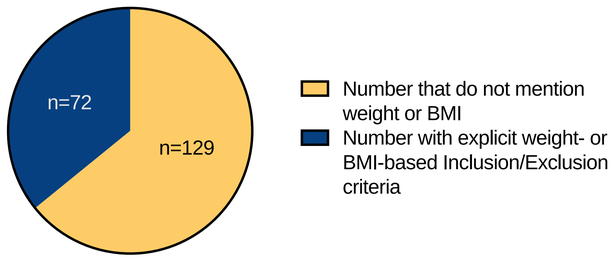

Figure 1. Of 201 drug approval studies in clinicaltrials.gov in 2022, 64% did not include weight- or BMI-based Inclusion/Exclusion criteria, which does not ensure the inclusion of people with obesity in these studies.

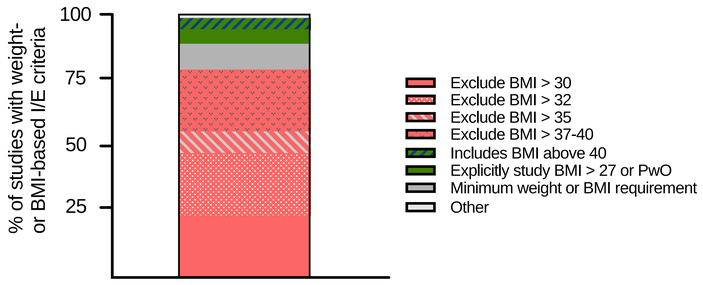

Figure 2. Of the studies that do have weight- or BMI-based Inclusion/Exclusion criteria, the criteria were used to Exclude patients with obesity for more than 75% of the trials.

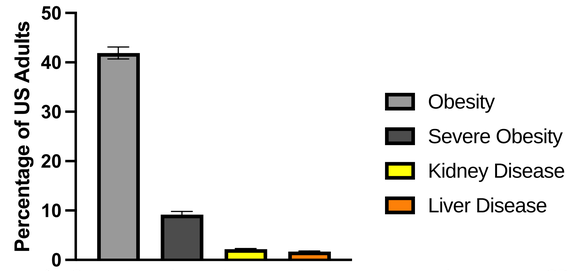

Figure 3. Percentage of US Adults with selected diseases, according to the CDC. Patients with kidney disease or liver disease are routinely included in drug approval clinical trials.

Table 1. Examples of drugs with actionable changes for people with obesity

Drug Name	Common Use	Relevance for Patients	Current Dosing Recommendation*	Proposed Instructions for People With Obesity
Brexpiprazole	anti-psychotic	Increased half-life leads to significantly longer time to attain effective plasma concentrations	Schizophrenia: Initiate dosing at 1 mg qd for three days, increase to 2 mg qd for four days, then increase to 4 mg qd thereafter as tolerated	Schizophrenia: Initiate dosing at 1 mg bid for three days, increase to 2 mg bid for four days, then increase to 4 mg qd thereafter as tolerated
Vortioxetine	anti-depressant	Increased half-life leads to onger washout required to reduce risk of serotonin syndrome before switching to an MAOI	Wait at least 21 days after stopping vortioxetine before transitioning to an MAOI	Wait at least 31 days after stopping vortioxetine before transitioning to an MAOI
Posaconazole	anti-fungal	Increased half-life leads to increased risk of drug-drug interactions after stopping posaconazole	None	Require a washout period after stopping posaconazole before resuming normal CYP3A4 substrate drug administration
		Lower plasma concentrations may need increased dose for effectiveness	Monitor patients for fungal infection	For treatment of fungal infections with IV posaconazole: Increase loading dose and daily maintenance dose to 400 mg in patients who weigh over 140 kg
Cefazolin	antibiotic	Lower tissue concentrations may increase risk of undertreatment of infection	1-2 g IV prior to incision, with 500 mg - 1 g IV every 6-8 h post-operatively	2 g IV given prior to incision, with 2 g IV every 4-6 h post-operatively
Tacrolimus	immunosuppresssant	Overdose upon tacrolimus initiation may increase risk of toxicity	Initiate dosing on a mg/kg basis [based on total body weight]	Calculate initial dose on a mg/kg basis using IBW
Levonorgestrel (Plan B)	emergency contraception	Less effective in patients over 70 kg; higher risk of pregnancy	None	Patients over 70 kg (150 lb) should use an alternative form of emergency contraception

* as described by the package insert instructions
qd, once daily; bid, twice daily; IBW, ideal body weight; IV, intravenous; MAOI, monoamine oxidase inhibitor

Conclusions

There is currently no requirement to test drugs in people with obesity during the drug approval process, even when preliminary data suggests there may be altered kinetics in this population. When clinical trials Include or Exclude patients based on weight or BMI, people with obesity are Excluded from over 75% of trials. The lack of information, and subsequent underappreciation by clinicians and caretakers, on the safe and effective use of drugs in people with obesity may be contributing to poorer health outcomes in this population.

Incomplete Data and Potential Risks of Drugs in People with Obesity

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