IPWSO
International
Prader-Willi Syndrome
Organisation

Is there a role for GLP-1 Receptor Agonists in Prader-Willi Syndrome?

Glucagon Like Peptide-1 (GLP-1) is a hormone released by the gastrointestinal tract (gut) in response to the presence of food that stimulates insulin release to regulate blood glucose (i.e., blood sugar) levels. It does this through binding to specialized GLP-1 receptors found in tissues throughout the body including the pancreas, gut, heart, liver, as well as nerves and brain centers that regulate appetite and hunger. GLP-1 release and binding to GLP-1 receptors signals to the brain that food has been consumed and appetite should be reduced.

Medications, called agonists, have been developed to directly activate GLP-1 receptors (GLP-1 RAs) which have been shown to improve control of blood sugar levels, decrease appetite and encourage weight loss in the typical, non-Prader-Willi syndrome (non-PWS) population. This discovery has generated enthusiasm among the Prader-Willi syndrome (PWS) community searching for treatment options to alleviate the relentless hyperphagia experienced by individuals with PWS.

One way that GLP-1 RAs decrease appetite is through slowing movement of the gut which can lead to side effects. Nausea and abdominal discomfort are common side effects, but there have been less common, more severe complications. GLP-1 RAs medications can cause stomach contents to back up into the throat where they may be inhaled into the lungs (pulmonary aspiration). Gut movements can become slowed to the point that blockages develop and rupture. The gut can also become paralyzed (gastroparesis) stopping all bowel movements.

Individuals with PWS already have abnormally high rates of these specific gut problems which, when combined, account for 10% of deaths in PWS (3rd leading cause). Individuals with PWS are less likely than the non-PWS population to experience nausea and vomiting which are the first indicators of decreased gastric emptying, making it harder to detect serious side effects. GLP-1RA also increase the risk for inflammation of the pancreas and kidney. These serious, potentially life-threatening side effects must be considered when deciding to use, or not use, GLP-1 RAs in PWS.

But the most important question to answer is: Do GLP-1 RAs medications actually work in PWS? At this time in our exploration, we do not have a clear answer to this question. Very few of the "Gold Standard", double-blind, randomized clinical trials of GLP-1 RAs have focused on effects in PWS. Most scientific reports in PWS were small, narrow in scope, used open-label (unblinded) study designs, and often examined extremely complex cases of critically ill individuals.

A summary of the consistent findings in PWS do support a modest clinical benefit of GLP-1 RAs for control of blood sugar – as indicated by reductions in blood levels of A1c. But the effects of GLP-1 RAs on other important metrics in PWS such as appetite, satiety, body mass, and body composition have been highly variable and modest, falling short of the robust effects observed in the non-PWS population. More focused studies are needed to conclusively define these effects and rates of specific side effects in PWS.

In summary, current evidence does not support a clinical benefit for GLP-1 RAs to reduce appetite, hunger, or body mass in PWS.

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