Classification of Non-Insulin Glucose Lowering Drugs

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Abstract

The ever-changing scenario of diabetes care, especially pharmacotherapy, calls for a framework to help classify non-insulin glucose drugs. Such a taxonomic structure should be of contemporary relevance as well as futuristic in vision; scholarly in intent but easy to understand; and based on pathophysiologic principles while being useful for the clinician. We propose a rubric which lists four classes of non-insulin glucose lowering drugs; insulin secretagogues, insulin sensitizers, calorie restriction mimetics, and calorie restrictors. This classification serves the need of students and teachers as well as pharmacologists and clinicians alike.

Keywords: Alpha glucosidase inhibitors, DPP4i, GLP1RA, liraglutide, pharmacotherapy sulfonylureas, semaglutide, SGLT2i.

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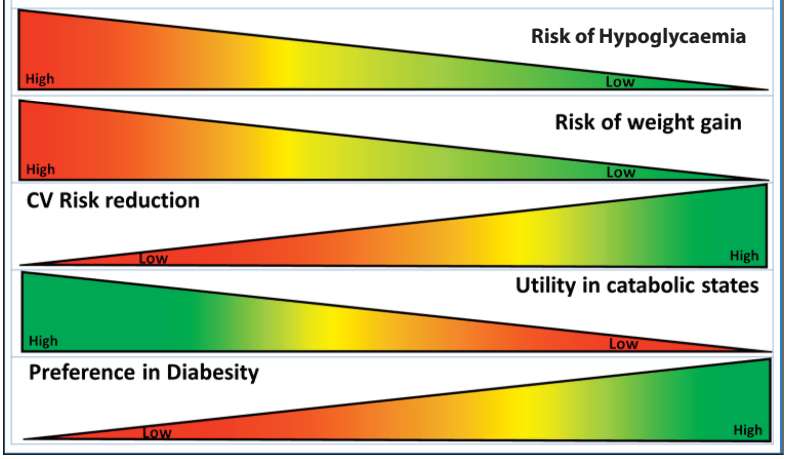
Table: Classification of non-insulin glucose lowering therapy.

Insulin Secretagogues	Insulin Sensitizers	Calorie Restriction Mimetics (CRMs)	Calorie Restrictors & CRMs
Direct: • **Sulfonylureas**	Conventional: • Metformin • Pioglitazone	Acting on Urinary tract: • SGLT2i	Dual Agonists*
Indirect: • **DPP4i, GLP1-RAs**	Modern: • GLP1-RAs	Acting in the gut: • AGIs, GLP1-RAs	Intermediate & long acting GLP1-RAs



Introduction

Changes in diabetes pharmacotherapy continue to challenge existing dogmas, and expand our thought process. The last decade has seen diabetes care guidelines evolve and improve, with advances in our understanding of pathophysiology as well as therapeutic targets.[1] Enhanced awareness about the targets of glucose control, as well as betterment of the tools and techniques utilized to achieve these aims, have led to a change in the way some drugs are used.[2] Newer research has also unearthed novel mechanisms of action of existing medications.

The classification of non-insulin glucose lowering drugs, proposed in 2015, still remains the most updated taxonomic model in its field.[3] It structures all such drugs as insulin sensitizers, insulin secretagogues, and nutrient load reducers. Based upon mechanism of action, it facilitates the apt choice of therapy, by matching pharmacodynamic properties with potential targets of action.[1,4]

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Contemporary Classification

We therefore suggest a contemporary classification, to facilitate rational prescription of glucose lowering drugs, and their combinations. Less frequently used drugs have been omitted from the table, to simplify the structure, and make it reader-friendly as well as practice-oriented. Drugs which are expected to gain regulatory approval in the coming years have been added, with an asterisk, to ensure relevance of our rubric in the coming decade.

The new classification is a tabular list of four classes: insulin secretagogues (direct and indirect), insulin sensitizers (conventional and modern), calorie restriction mimetics (acting on the urinary tract and gut), and calorie restrictors (acting on the gut-hypothalamus axis).[5] It must be noted that the GLP1-RA class finds a mention in all four lists, due to its multifaceted action. All GLP1-RAs, including liraglutide, dulaglutide and semaglutide have differing properties, which are highlighted in the table.[6]

The calorie restriction mimetic category has been

separated from the true "calorie restrictors". GLP1RA, and GLP1-based dual agonists, act upon the hypothalamus to reduce appetite, and thus restrict calories, apart from mimicking calorie restriction.[7-9] Hence, they are listed separately from SGLT2i and AGIs.

Utility of the current classification

The horizontal format of the taxonomic rubric works as an aid to clinical decision making. The four classes are listed according to their risk of hypoglycaemia, impact on weight loss and cardiovascular risk reduction, and utility in "maladaptively anabolic" versus catabolic diabetes states. This helps in placement of drug classes, individual drugs, and their combinations, while planning therapy.

The contemporary classification that we propose, therefore, is an improvement over earlier taxonomic effort. It facilitates understanding of the subject serves as an aid to clinical decision-making, and bridge the gap between theory and practice. The ease of reading and remembering the model will endear it to students and experts alike. At the same time, inclusion of futuristic molecules should ensure its utility in the years to come.

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