

Sodium-glucose Cotransporter 2 Inhibitor Use: A Pharmaco-ergonomic Qualification Tool

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Abstract

Pharmaco-ergonomics implies tailoring the drug therapy to an individual patient's requirement(s). The development of sodium-glucose cotransporter 2 inhibitor (SGLT2-i) agents has impelled multiple clinical considerations, in the management of type-2 diabetes. This paper attempts to summarize the pharmaco-ergonomic considerations for these agents, in the form of an SGLT2-i qualification tool, based on a clinical score. This tool may serve as a simple and inexpensive practical guide, to optimize the risk-benefit considerations for SGLT2-i agents.

Keywords: Pharmaco-ergonomics, sodium-glucose cotransporter 2 inhibitor clinical score, sodium-glucose cotransporter 2 inhibitor qualification tool

INTRODUCTION

Progress in medical science has resulted in the availability of diverse therapeutic options for the management of type-2 diabetes mellitus (T2DM). In contemporary diabetology, the relative abundance of options has resulted in a pleasant problem of plenty. To take an optimistic view, this is an opportunity for providing better care; however, to realize this opportunity, physicians need detailed study of pharmacology.

“Pharmaceutical pluralism” may sometimes provoke rather unfavorable consequences. “Paradox of plenty” is one such phenomenon described in economic parlance, which suggests that overreliance on an abundantly available resource could result in adverse developmental outcomes.^[1] This phenomenon is a reality in medical science, which tries to balance evidence-based medicine, on the one hand, with personalized medicine, on the other. Both these viewpoints are not necessarily antagonistic, however. To achieve concordance between these two management approaches, the perspective of “pharmaco-ergonomics” deserves our attention.

PHARMACO-ERGONOMICS

“Ergonomics” is a scientific discipline, concerned with the understanding of interactions among human beings and the other elements of a system.^[2] The concept of pharmaco-ergonomics

represents the science and art of tailoring drug therapy to the appropriate patient characteristics. While this concept has been previously stated in the context of human genotype,^[3] it may well be extrapolated to the patient phenotype.

A pharmaco-ergonomic approach implies prescription of the most effective choice of therapeutic drugs, in the most efficient manner. This paraphrases the need for contemporary providers of diabetes care to prescribe “patient-centered care,” on the basis of an individual person's requirements. A phenotype-based, pharmaco-ergonomic approach implies prescription of the most effective and efficient therapeutic choice, based on analysis of the phenotypic features of the patient. This is especially important in diabetes management as inappropriate therapeutic decisions may lead to unwanted glycemic burden and to promote the development of complications.

CLINICAL GLIFLOZIN-LOGY

The development of sodium-glucose cotransporter 2 inhibitor (SGLT2-i) agents has changed management patterns

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in diabetology. Their unique pharmacological and clinical features merit a holistic pharmaco-ergonomic assessment to optimize their use. The safe and pragmatic clinical use of gliflozins has been elaborated previously.^[4]

Advantages

These agents reduce fasting as well as prandial glycemia. These agents also consistently demonstrate reduction in body weight, as well as in blood pressure. Some cases of difficult-to-treat hypertension may respond to SGLT2-i agents.^[5] A reduction in plasma uric acid levels has also been consistently demonstrated with this class of drugs.

As add-on options to metformin, empagliflozin has demonstrated preservation of renal function over 4 years, as compared to glimepiride.^[6] An insulin-sparing effect has also been recognized with these agents although these should not be considered as insulin substitutes.

Apart from these effects, the EMPA-REG outcome study has demonstrated a clinically meaningful reduction in cardiovascular mortality in patients of T2DM with cardiovascular disease.^[7] This cardiovascular protection was evident with empagliflozin, on the top of the current standard cardioprotective therapies.

Indeed, despite advances in the cardioprotective approaches such as statin and aspirin prophylaxes, cardiovascular disease still accounts for the majority of deaths in T2DM. This considerable residual cardiovascular risk in type-2 diabetes remains to be addressed with the current standard of care therapies.^[8] These cardioprotective advances demonstrated with empagliflozin, and subsequently with liraglutide and semaglutide, have impelled broadening of clinical perspective from a mere glucocentric focus, to a more optimal cardiocentric approach in managing T2DM.^[9,10] Further qualitative research is also exploring the renoprotective and hepatoprotective aspects of these agents.

Limitations

At the same time, there are safety concerns associated with gliflozin use. These obligate a clinician to appraise each patient, to rule out ineligibility, or identify high risk for drug-associated complications, before starting SGLT2-i therapy. Safety considerations for SGLT2-i agents are largely dependent on the characteristics of the patient.^[4] In patients having a history of recurrent urinary tract infections (UTIs), the risk of UTI may be increased. Volume depletion-related adverse events may be more frequently observed in frail elderly patients, in conditions of fluid loss, or with concomitant use of loop diuretics. In lean and undernourished patients who may harbor considerable β -cell dysfunction, or in patients with severe illness, or those having a high metabolic rate, the risk of euglycemic diabetic ketoacidosis (euDKA) merits an obvious consideration. Similarly, conditions of starvation, excessive alcoholism, or dehydration may increase the risk of euDKA with these agents. These agents should be discontinued 2–3 days before any planned stressful event, surgery, or radiocontrast studies.

In patients having hypovolemia, hypotension, or elevated hematocrit, the use of these agents may be avoided.

Certain considerations, such as an increased risk of bone fractures or toe amputations, have been evident specifically with canagliflozin, whereas cases of acute renal impairment have been observed with all the SGLT2-i agents. Concomitant use of these agents with loop diuretics may increase the risk of hypovolemia; hence, the dose of loop diuretics may be down-titrated. On concomitant use with insulin or insulin secretagogues, the risk of hypoglycemia may increase. Hence, the dose of insulin needs to be gradually down-titrated. It must be remembered that these agents do have an insulin-sparing effect; however, these should not be used as substitutes for insulin. The concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with these agents.

In simple terms, the 7-D mnemonic helps define people at high risk of complications with SGLT2-i therapy as described in Table 1.

THE SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR QUALIFICATION TOOL

In line with the concept of pharmaco-ergonomics, we propose an SGLT2-i qualification tool, as a low-cost, yet effective, phenotype-based approach, to optimize risk-benefit outcomes in persons with T2DM.

Based on the phenotypic characteristics of persons with type 2 diabetes, clinical considerations which determine the use of SGLT2-i agents are summarized in Table 2.

This pharmaco-ergonomic qualification tool is an attempt to optimize use of SGLT2-i agents, by suggesting the risk-benefit of various clinical situations. The first column of our tool offers a simple classification of all phenotypic variables, listing them as demographic, metabolic, cardiovascular, renal, and comorbid conditions [Table 2]. The five phenotypic characteristics of the patients are further classified into three color-coded categories.

The red category indicates absolute contraindications for using SGLT2-i agents. Any single characteristic of the patient, which falls in the red category, should prompt avoidance of or immediate discontinuation of SGLT2-i

Table 1: Risk of complications with sodium-glucose cotransporter-2 inhibitor therapy: 7 Ds

| |
|--------------------------------------------------------------------------------------|
| D: Duration of age |
| D: Debilitated state |
| D: Dehydration |
| D: Digit ischemia |
| D: Deranged renal function (eGFR <45 mL/min/1.73 m ²) |
| D: Diuretic, loop |
| D: Damaging agents for kidneys (NSAIDs, radiocontrast) |
| NSAIDs: Nonsteroidal anti-inflammatory drugs, eGFR: Epidermal growth factor receptor |

Table 2: Pharmaco-ergonomic qualification of sodium-glucose cotransporter-2 inhibitor agents

| Phenotype | Evident benefit | Benefit to risk ratio must be considered | Contraindications |
|--------------------------------|--------------------------------------------|-----------------------------------------------|-------------------------------------------------------------|
| Demographic | Young/middle-aged patient | Elderly patient | Pregnancy/lactation; age <18 years |
| Metabolic | Overweight Obesity | Normal weight | Lean patients; starvation; frailty |
| Cardiovascular and hemodynamic | CVD/risk factors and hemodynamic stability | Risk of volume-depletion | Acute CVD; hemodynamically unstable; elevated hematocrit |
| Renal | Stable CKD; risk-factors for CKD | History of recurrent Urogenital infections | Acute renal impairment; eGFR <45 mL/min/1.73 m ² |
| Comorbid | Healthy patient | Concomitant therapy (NSAIDs, loop diuretics) | Acute medical/surgical illness |

CKD: Chronic kidney disease, CVD: Cardiovascular disease, NSAIDs: Nonsteroidal anti-inflammatory drugs, eGFR: Epidermal growth factor receptor

therapy in that individual. The orange and green categories include the phenotypic characteristics, which prompt a possible consideration for an SGLT2-i-based therapy. The orange category represents those characteristics for which the risk versus benefit should be considered more critically, as compared to the green category.

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR CLINICAL SCORE

Further, a simple clinical score may be applied to provide an objective value to the phenotype based pharmaco-ergonomic tool. For each of the five phenotypic categories listed, the patient's respective characteristics may be scored as:

- Green category: 1 point
- Orange category: 0 point
- Red category: Any characteristic in the red category suggests absolute contraindication for SGLT2-i therapy, regardless of the overall score of the patient.

The score for each phenotypic category may be added up (with a maximum possible score of 5 and a minimum of 0). The interpretation of the added score may be as follows:

- 3–5: Benefits of SGLT2-i therapy outweigh the risks
- 0–2: SGLT2-i therapy may be considered only if appropriate risk mitigation is possible
- Any characteristic in red category, regardless of the total score denotes: Risks of SGLT2i therapy outweighs the benefits, the use of SGLT2i therapy should be avoided.

CONCLUSIONS

The SGLT2-i agents promise a paradigm shift in the management of type-2 diabetes, from the conventional glucocentric approach to a more holistic metabolic and cardiocentric approach. Their pharmacological properties, however, require a clinical assessment before prescription. The SGLT2i qualification tool proposed in this article is

based on sound phenotypic pharmaco-ergonomic principles. The tool is simple and inexpensive to use and should be of value to both practitioners and students of diabetology. While the score remains to be scientifically validated, this tool will serve as a clinical aid to decision-making, to minimize risks and in turn maximize possible benefits associated with the use of SGLT2-i agents.

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Conflicts of interest

There are no conflicts of interest.

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