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Original Research Article

Prescribing complexity of oral hypoglycemic fixed-dose combinations in India: development and application of a novel complexity scoring tool

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ABSTRACT

Background: Fixed-dose combinations (FDCs) of oral hypoglycemic agents are extensively used in India for simplifying type 2 diabetes mellitus (T2DM) treatment and improving adherence. There are long-standing concerns regarding irrational FDCs, limited dose flexibility, and weak alignment with clinical guidelines. Currently, no structured framework exists to assess the prescribing complexity of these FDCs. Objectives of the study were to characterize oral hypoglycemic agent FDCs approved and marketed in India and to develop and apply a novel prescribing complexity score for oral hypoglycemic fixed-dose combinations (PCS-OHA-FDC).
Methods: A secondary analysis of oral hypoglycemic agent FDCs approved by the Central Drugs Standard Control Organization and listed in standard drug information sources was conducted. Each FDC was evaluated across four domains: number of active pharmaceutical ingredients, therapeutic duplication, dose flexibility, and guideline concordance. Domain scores were summed to derive an overall prescribing complexity score and to classify FDCs as low, moderate, or high complexity.
Results: 57 OHA FDCs were included in the analysis. Two-drug FDCs constituted the majority (40/57; 70.2%), while there were 17 three-drug FDCs (29.8%). No FDC demonstrated direct therapeutic duplication. Limited dose flexibility (7/57; 12.3%) and conditional or absent guideline support (40/57; 70.17%) was common. Using the prescribing complexity score for OHA-FDCs (PCS-OHA-FDC), most formulations were classified as low complexity (42/57; 73.68%), with the remainder showing moderate complexity (15/57; 26.31%). No FDC met criteria for high prescribing complexity.
Conclusions: The PCS-OHA-FDC offers a practical tool to quantify prescribing complexity and highlights important gaps between market availability and guideline-based diabetes care in India.

Keywords: Fixed-dose combinations, Oral hypoglycemic agents, Prescribing complexity, Rational drug use, India

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has emerged as a growing public health concern in India. Most patients require long term treatment with oral hypoglycemic agents (OHAs). This is often fraught with practical difficulties of increased pill burden and lack of treatment adherence, particularly when combination therapy with OHAs become necessary. To overcome this difficulty, clinicians now increasingly prescribe Fixed dose combinations (FDCs) of OHAs.[1]

The recent years have witnessed a rapid increase in the number of OHA FDCs available in the Indian market. These include combinations of older OHAs such as biguanides and sulfonyl urea's as well as newer drug classes such as sodium–glucose co-transporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors. The expanding range offers more therapeutic options, but raises concerns about irrational combinations, variable alignment to treatment guidelines and lack of dose flexibility.[2] Such concerns have prompted periodic regulatory reviews by

Central Drugs Standard Control Organization (CDSCO) particularly in regard to irrational combinations.[3]

Prescribing complexity is an important aspect of rational drug therapy with OHAs. The complexity is not only influenced by the number of drugs combined but also factors such as overlapping therapeutic actions, limited scope for dose individualizations and adherence to treatment guidelines.[4,5] Although these issues of prescribing complexity are often discussed in qualitative terms, there is currently no simple or reproducible method to quantify prescribing complexity of OHAs.

Our present study aimed to develop and apply a novel prescribing complexity score for oral hypoglycemic fixed-dose combinations (PCS-OHA-FDC) using publicly available secondary data. By systematically assessing the complexity of marketed OHA FDCs in India, this study aims to support more informed prescribing, regulatory evaluation, and policy discussions around rational OHA FDC use.

METHODS

Study design and data sources

This study was a cross-sectional secondary analysis of oral hypoglycemic FDCs marketed in India. The primary data source was publicly accessible regulatory data from CDSCO.[6] The lists of all approved OHA FDCs was obtained from the CDSCO database.[7] The data was cross verified with standard drug compendia to ensure completeness and for ensuring market availability.[8]

Identification and classification of oral hypoglycemic FDCs

All marketed oral hypoglycemic FDCs listed during the study period were screened. Each unique FDC formulation was considered as a single analytical unit, irrespective of the number of marketed strengths. Parenteral formulations, insulin-containing products, and nutraceutical combinations were excluded.

For each eligible FDC, the following information was extracted: constituent active pharmaceutical ingredients (APIs), pharmacological class of each API, number of APIs, marketed strengths, and formulation characteristics relevant to dose adjustment.

Development of the prescribing complexity score for oral hypoglycemic FDCs (PCS-OHA-FDC)

A novel, domain-based prescribing complexity score for oral hypoglycemic fixed-dose combinations (PCS-OHA-FDC) was developed to quantify prescribing complexity in a structured and reproducible manner. The tool was designed a priori based on established principles of rational pharmacotherapy, guideline-based diabetes management, and prescribing safety.

The PCS-OHA-FDC comprises four predefined domains: number of active pharmaceutical ingredients (APIs), therapeutic duplication within the combination, dose flexibility, and guideline concordance. Each of these domains were assigned an ordinal score. Increasing score reflected increasing prescribing complexity. FDC domain scores were then summed and total prescribing complexity score (PCS score) was calculated. Higher scores indicated greater prescribing complexity. Based on the total PCS score and pre-specified cut-offs, FDCs were categorized into low, moderate, or high-complexity groups.

Operational definitions of PCS domains

Therapeutic duplication was assessed within an FDC by identifying overlap in pharmacological mechanism of actions. Duplication was categorized as none, partial, or direct. Dose flexibility was classified as high, moderate, or low depending on the availability of multiple strength combinations that allow independent titration of individual components.

Guideline concordance was evaluated with reference to contemporary diabetes treatment guidelines, including Indian and international recommendations.[9-11] FDCs were categorized into guideline-concordant, conditionally recommended, or not recommended based on the therapeutic recommendations.

Validation of the PCS-OHA-FDC

Structured face and content validation was done prior to application. Review for domain selection and scoring logic to assess clinical relevance, clarity, and internal coherence was done independently by pharmacology and clinical experts. The framework of the PCS-OHA-FDC was iteratively refined for ensuring that each domain captured a distinct and meaningful contributor to prescribing complexity. Construct validity was assessed by examining whether higher PCS scores aligned with combinations known to pose greater challenges in clinical practice. For e.g. three-drug FDCs with limited dose flexibility or weaker treatment guideline support. The validation process and scoring workflow are illustrated in the PCS development figure.

Statistical analysis

Data were entered into Microsoft excel and analyzed using descriptive statistics. Categorical variables were summarized as frequencies and percentages. Continuous variables were summarized using medians and ranges. The distribution of PCS categories was examined across different FDC characteristics such as number of APIs, drug classes, dose flexibility, and guideline concordance. As the aim of the study was to describe prescribing complexity, no inferential statistical testing was performed. All the statistical analyses were conducted according to a pre-specified analytical plan for ensuring transparency and reproducibility.

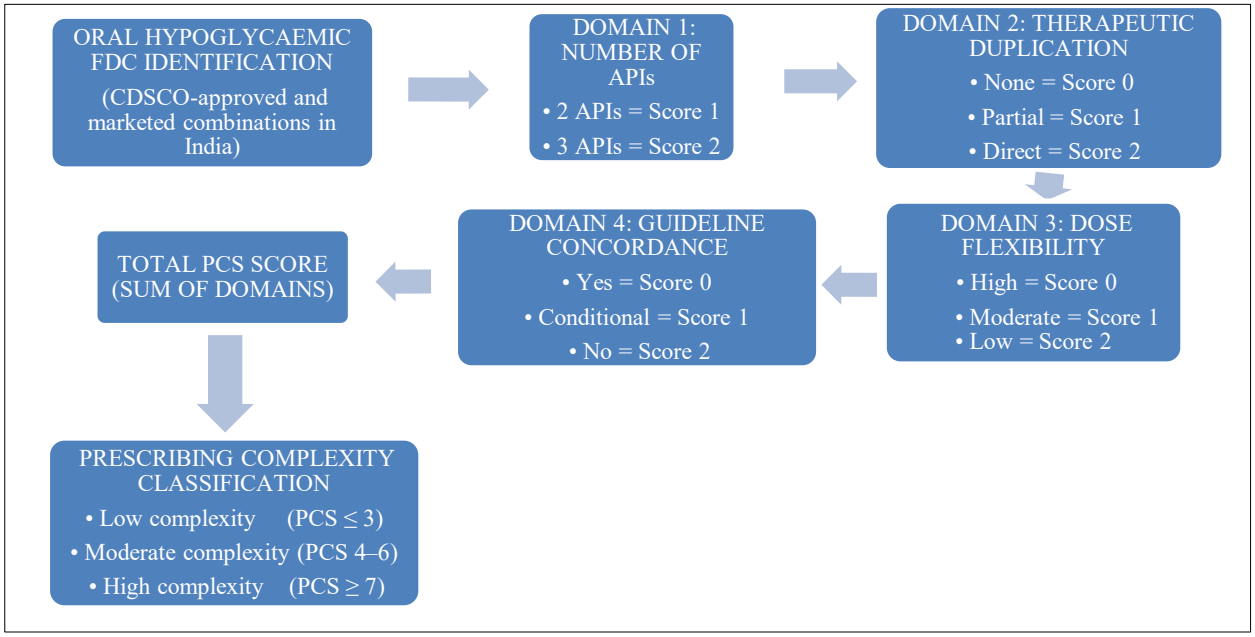

Figure 1: Prescribing complexity score for oral hypoglycemic fixed-dose combinations (PCS-OHA-FDC).

RESULTS

A total of 57 oral hypoglycemic fixed-dose combinations (FDCs) approved for use in India were identified and analyzed. Two-drug combinations constituted the majority of formulations (40/57; 70.17%), while three-drug FDCs accounted for nearly one-third (17/57; 29.82%) (Table 1).

No formulation demonstrated therapeutic duplication, indicating that all included drugs belonged to distinct pharmacological classes. Dose flexibility varied considerably across OHA FDCs. Approximately half of the formulations allowed high dose flexibility (29/57; 50.87%), whereas 12% FDCs had limited flexibility (7/57). 29.82% FDCs were fully concordant with guideline-recommended treatment (17/57; 29.82%). A substantial proportion were only conditionally recommended (27/57; 47.36%), and almost one-quarter lacked guideline support. (13/57; 22.80%) (Table 1). Metformin was included in 68.42% of FDCs (39/57). Newer antidiabetic drug classes such as DPP-4 inhibitors were included in 50.88% of all FDCs (29/57) and SGLT2 inhibitors in 40% (23/57) FDCs (Table 1).

Assessment using the prescribing complexity score for oral hypoglycemic FDCs (PCS-OHA-FDC) showed that most formulations were associated with low prescribing complexity (42/57; 73.68%) (Table 2). The median PCS score was 3 (interquartile range: 2–4). Moderate complexity was observed in 15 formulations (26.31%), while none met criteria for high complexity.

Table 1: Characteristics, guideline concordance, and prescribing attributes of oral hypoglycemic FDCs (n=57).

Parameter	Category	N	%
Number of APIs	Two-drug FDCs	40	70.17
	Three-drug FDCs	17	29.82
Therapeutic duplication	None	57	100
	Partial/direct	0	0
Dose flexibility	High	29	50.87
	Moderate	21	36.84
	Low	7	12.28
Guideline concordance	Yes	17	29.82
	Conditional	27	47.36
	No	13	22.80
Major drug-class backbone	Metformin-containing FDCs	39	68.42
	Non-metformin FDCs	18	31.57
Newer antidiabetic agents	SGLT2 inhibitor–containing	23	40.35
	DPP-4 inhibitor–containing	29	50.88

SGLT2: sodium–glucose cotransporter-2; DPP-4: dipeptidyl peptidase-4. Percentages calculated out of total FDCs (n=57).

Table 2: Prescribing complexity score (PCS-OHA-FDC) distribution of oral hypoglycemic FDCs (n=57).

PCS domain	Category	N	%
Total PCS score	Median (IQR)	3 (2-4)	-
Complexity category	Low complexity (PCS ≤3)	42	73.68
	Moderate complexity (PCS 4–6)	15	26.31
	High complexity (PCS ≥7)	0	0
API-driven complexity	Two-drug FDCs	40	70.17
	Three-drug FDCs	17	29.82
Drivers of higher PCS	Low dose flexibility	7	12.28
	Guideline non-concordance	13	22.8
Highest PCS observed	PCS=6	2	3.50

PCS-OHA-FDC: Prescribing complexity score for oral hypoglycemic fixed-dose combinations

Three-drug FDCs contributed disproportionately to higher PCS values. The highest PCS score observed was 6, identified in a small subset of three-drug combinations incorporating older glucose-lowering agents (2/57; 3.50%) (Table 2).

DISCUSSION

This study provides a structured and transparent assessment of prescribing complexity of OHA-FDCs available in the Indian pharmaceutical market. A newly developed prescribing complexity score for OHA-FDCs (PCS-OHA-FDC) was employed for this analysis. The analysis demonstrates that most of the OHA FDCs fall within the low to moderate prescribing complexity range. This may be attributed to the predominance of two drug OHA FDCs, absence of direct therapeutic duplication and a broad alignment with contemporary type 2 diabetes mellitus treatment guidelines.[9]

In this study metformin based dual FDCs especially those paired with SGLT2 inhibitors or DPP-4 inhibitors consistently exhibited lowest complexity scores reflecting their contemporary guideline concordance, high dose flexibility and complimentary mechanism of action. These findings align with current national and international diabetes treatment guidelines which recommends metformin as foundational therapy and early addition of SGLT2 inhibitors or DPP-4 inhibitors according to patient specific factors. In contrast FDCs with older OHAs such as thiazolidinediones, meglitinides, or alpha-glucosidase inhibitors showed conditional or no concordance with treatment guidelines contributing to higher PCS scores.[9-11]

Three drug OHA FDCs showed an increase in prescribing complexity owing to their reduced dosing flexibility and challenges in individualizing treatment. Several three drug OHA FDCs with sulfonylureas and thiazolidinediones as ingredients showed moderate prescribing complexity scores underscoring potential concerns of increased risk of hypoglycemia, weight gain and limited dose individualization options. No FDC in the dataset demonstrated direct therapeutic duplication, which is indicative of lack of role of irrational duplication in complexity of current Indian OHA-FDC landscape. Prescribing complexity was primarily influenced by guideline discordance and lack of flexibility in dosing.[12]

PCS-OHA-FDC offers a pragmatic tool for comparing FDCs beyond simple drug counts. The tool incorporates pharmacological, regulatory, and guideline-based considerations into a single composite score. The score facilitates identification of FDCs that require closer clinical scrutiny especially when prescribing decisions are made considering patient preference, availability and cost rather than guideline recommendations. In the Indian context where FDCS are often preferred to reduce pill burden and increase affordability, PCS-OHA-FDC can help in assisting prescribers and regulators in balancing simplicity and rationality when choosing FDCs.

Limitations

This study has several limitations. First, this is a secondary analysis based on publicly available data of approved and marketed FDCs and does not account for real word prescribing frequencies, adherence or outcomes. Second, guideline concordance was measured using broad treatment guidelines and hence may not capture nuanced patient specific clinical justifications for prescribing certain FDCs. Third, dose flexibility was assessed from available marketed strengths rather than real world dose titration practices. Finally, the PCS-OHA-FDC has not yet been externally validated against clinical outcomes, prescriber behavior, or patient-level complexity measures. Validating the PCS-OHA-FDC scores in clinical settings and exploring the score association with safety and effectiveness is needed

CONCLUSION

The PCS-OHA-FDC tool provides a novel reproducible and policy relevant framework for evaluating prescribing complexity of OHA FDCs in India. While the majority of marketed FDCs demonstrated low prescribing complexity and alignment with guidelines, a subset of triple drug FDCs and FDCs with older OHAs exhibited comparatively higher complexity profiles. Incorporation of PCS-OHA-FDC tool in pharmacoepidemiologic research, formulary

decisions, and prescriber education can support more rational and patient centered therapy with OHA FDCs.

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