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Original Research Article

A Comparative Rational Pharmacotherapeutic Research Analysis and a Systematic Review and Meta-Analysis on the Oral Hypoglycaemic Rational Pharmacotherapeutic Research in Metformin Monotherapy and Combination Therapy

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Conflict of interest: Nil

Abstract

Introduction: This comparative rational pharmacotherapeutic research analysis, and this systematic review and meta-analysis was conducted for reviewing with a well-organised methodology, along with thorough explanations and analyses of the medical study literature and evidence, compiled from the numerous studies conducted, which authenticated the systematic review and meta-analysis topic of the oral hypoglycaemic rational pharmacotherapeutic research on metformin.

Objective: The objective of this comparative rational pharmacotherapeutic research analysis, and systematic review and meta-analysis was the qualitative exploration of the oral hypoglycaemic rational pharmacotherapeutic research in metformin monotherapy and combination therapy, with quantitative interpretations.

Methods: The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration in June, 2016. At first, the steps of identification included the records which were identified through database searching and the additional records which were identified through other sources. This led to the steps of screening, which included the screened records after the duplicates were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, in the eligibility step, the full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons. This led to the final inclusion step, where the studies were included in the qualitative synthesis of a systematic review and meta-analysis, according to the inclusion criteria, and ultimately the studies were included in the quantitative synthesis.

Results: This systematic review and meta-analysis, contributed 2140 refined and relevant medical records, among total 2876 records obtained from the study databases search. It also comparatively analysed the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy, thus comprehensively explaining this evidence-based systematic review and meta-analysis.

Conclusions: To conclude, this comparative research analysis, and systematic review and meta-analysis provided the refined qualitatively synthesised medical records, study literature and

databases on the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy.

Keywords: Systematic Review, Meta-Analysis, Metformin, Oral Hypoglycaemics, Pharmacology, Clinical Pharmacology, Rational Pharmacotherapeutics.

Introduction:

Analysing in consideration of the rational pharmacotherapeutic significance of the initial anti-diabetic mono- as well as combination pharmacotherapy with metformin, for the treatment of type II diabetic patients, manifesting fresh symptoms, a sufficiently higher efficacious and safe recovery rate of patients are achieved, in routine anti-diabetic tertiary patient healthcare. Metformin also has an easy availability and quite convenient route of drug administration, with specific appropriateness for the initial and maintenance pharmacotherapy of different types of diabetic type II patients. The main mechanism of action of metformin is the gradual overwhelming of insulin resistance as well as causing hypoglycaemia, by activating the enzyme 5’ adenosine monophosphate, which catalyses the activation of protein kinase. Metformin, as its pharmacological co-therapeutic actions, also stabilises the HbA1c levels, along with reduction in weight, among these patients affected with diabetes associated obesity.

As to define a systematic review and meta-analysis, this unique clinical research method is a way of a detailed, systematic and interpretative method of collecting, assessing and synthesising the various medical evidence, to elaborate the research solution to a well-defined research question, in the form of a well-structured qualitative research review with quantitative analytical interpretations.

This systematic review and meta-analysis were conducted for reviewing with a well-organised methodology, along with thorough explanations and analyses of the medical study literature and evidence, compiled from the numerous studies conducted, which authenticated the systematic review and meta-analysis topic of the oral hypoglycaemic rational pharmacotherapeutic research on metformin.

Objective:

The objective of this comparative research analysis, and systematic review and meta-analysis is the qualitative exploration of the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy, with quantitative analytical interpretations.

Materials and Methods:

This study was a systematic review and meta-analysis and did not involve any human or animal subjects; therefore, it did not require any ethical approval, and, thus, was exempted from ethics review.

The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration in June 2016. At first, the steps of identification included the records which were identified through

database searching and the additional records which were identified through other sources. During this procedural step, any or all types of original research studies, systematic reviews, meta-analyses, case reports, case series, narrative reviews, study series, parallel studies and similar kind of studies or reviews, which are either qualitative, or quantitative, or both qualitative as well as quantitative, in their description of the investigative topic, were thoroughly analysed, with statistical interpretations. This led to the steps of screening, which included the screened records after the duplicates were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, in the next eligibility step, the selection criteria were examined.

The study selection criteria, for this systematic review and meta-analysis, were the following:

(a) The inclusion criteria were : The published articles on the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy; the original research studies, systematic reviews, meta-analyses, case reports, case series, narrative reviews, study series, parallel studies and similar kind of studies or reviews, of any or all types, which were either qualitative, or quantitative, or both qualitative as well as quantitative; the publication time-frame was chosen to be within a span of the past 5 years; any or all types of observational, descriptive and analytical research studies; and studies performed on any gender of patients.

(b) The exclusion criteria were: Irrelevant studies; studies older than 5 years; and the studies which were not based on the specific topic of oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy.

The full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons for exclusion. This led to the final inclusion step, where the studies were included in the qualitative synthesis of a systematic review, according to the inclusion criteria. Each study was assessed for allocation concealment, blinding, reporting of losses to follow-up or missing outcome assessments, evidence of important baseline differences between the groups, analysis on an intention-to-treat basis and use of a sample size calculation. After examining the relevance of the full articles, the medical data and evidences were independently obtained, using forms containing different determinant criteria of analyses, based on well-defined objectives, which were subsequently reviewed, to refine the medical databases and evidences, after elaborate multi-directional assessments. The medical data and evidences were extracted from the study resources, of heterogenous qualitative or quantitative nature, or both. Studies with any or all types of study characteristics and outcomes were obtained to derive the pertinent descriptive or analytical study literature, and subsequently certain selective investigative and experimental elucidations were chosen for elaboration, from the comprehensive review compilation of the published articles, to corroborate the analytical review of the clinical research study literature, databases and evidences on the analytical topic, which finally directed itself towards a well-structured comprehensive research interpretation of the overall study results, for a final specific conclusion. Ultimately the studies were included in the quantitative synthesis. Therefore, by the systematic review and meta-analysis, from the total initial study databases search records, the refined and relevant medical records were obtained, for the final analyses and interpretations. A comparative rational pharmacotherapeutic research analysis was

also performed for further elaboration of metformin rational clinical pharmacotherapeutics.

Results and Discussions:

Results:

(i) The results of this Systematic Review and Meta-Analysis were as follows: In this study, in the identification stage, the study literature search on the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy, contributed total 2876 records, among which 957 records were obtained in PubMed search, 468 records were obtained in EMBASE search, 789 records were obtained in Scopus search, and 662 records were obtained in additional databases search, identified through other sources. From these 2876 records, 334 duplicate records were removed. The total number of records, after removing these duplicate records, were 2542. In the screening stage, the records screened were 2542, from which 278 records were excluded, according to the exclusion criteria. Thus, in the eligibility stage, the full text articles assessed for eligibility were 2264, from which 124 full text articles were excluded, according to the exclusion criteria. In the final inclusion stage, the records ultimately included in the qualitative synthesis, according to the inclusion criteria, was 2140. These 2140 records were the refined contributions of this systematic review and meta-analysis. Thus, this systematic review and meta-analysis contributed 2140 refined and relevant medical records, among total 2876 records obtained from the study databases search, as depicted in Figure 1. **(ii) The selective investigative and experimental elucidations on the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy:** From the analytical compilation of pharmacotherapeutic databases and evidences, the selective investigative and experimental elucidations on the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy were also described, in complete details, to comprehensively explain the qualitative details of the conducted systematic review and meta-analysis.

Discussion:

In this evidence-based systematic review and meta-analysis, in the identification stage, the study literature search on the oral hypoglycaemic rational pharmacotherapeutic research on metformin, contributed total 2876 records, among which 957 records were obtained in PubMed search, 468 records were obtained in EMBASE search, 789 records were obtained in Scopus search, and 662 records were obtained in additional databases search, identified through other sources. From these 2876 records, 334 duplicate records were removed. The total number of records, after removing these duplicate records, were 2542. In the screening stage, the records screened were 2542, from which 278 records were excluded, according to the exclusion criteria. Thus, in the eligibility stage, the full text articles assessed for eligibility were 2264, from which 124 full text articles were excluded, according to the exclusion criteria. In the final inclusion stage, the records ultimately included in the qualitative synthesis, according to the inclusion criteria, was 2140. These 2140 records were the refined contributions of this systematic review and meta-analysis. Thus, this systematic review and meta-analysis contributed 2140 refined and relevant medical records, among total 2876 records obtained from the study databases search.

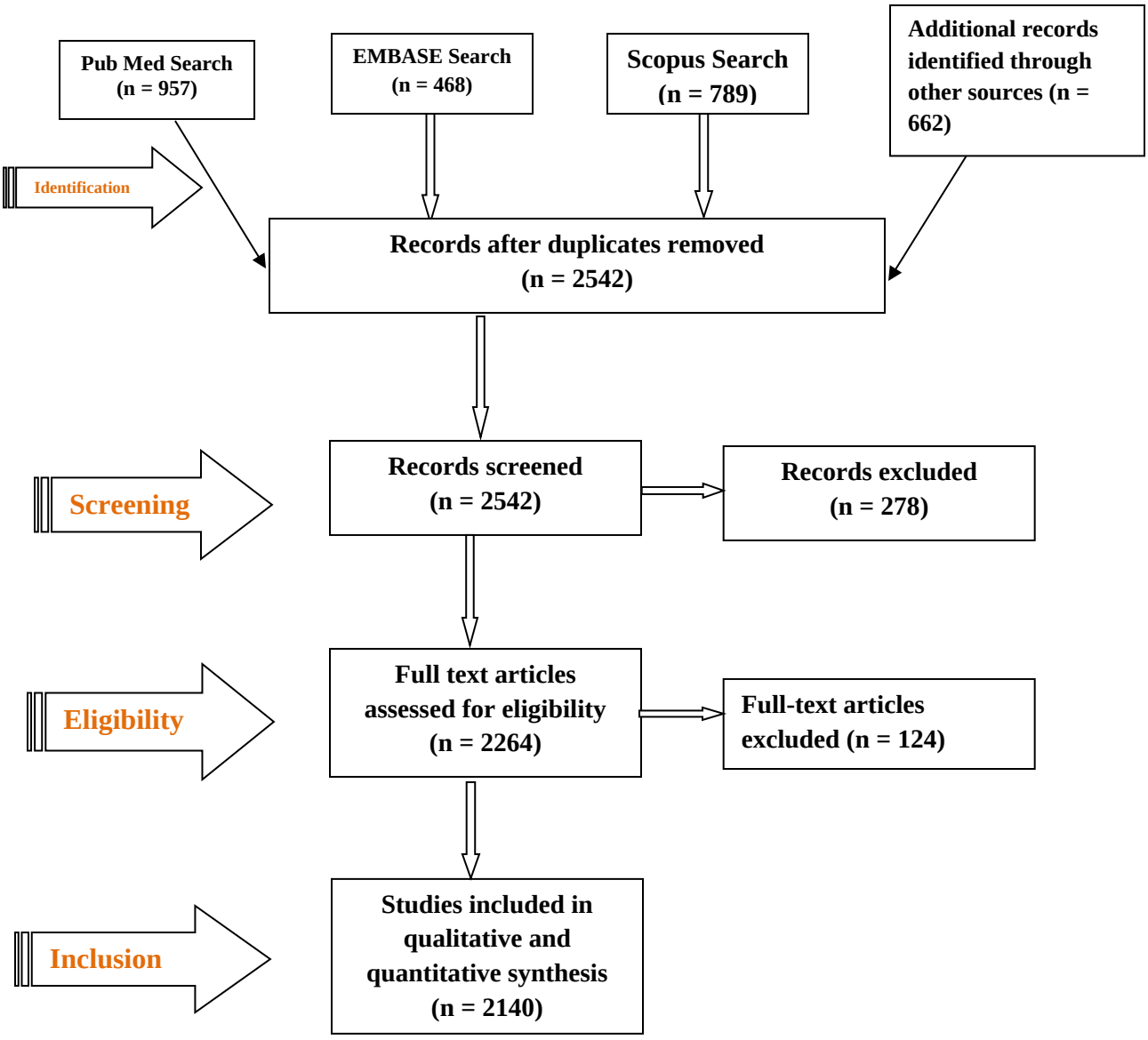

Figure 1: The Stages in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement and Guidelines, 2009

The selected qualitative investigative and experimental elucidations on the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy, were as following : From a study, it was obtained that the demographic characteristics of the patients were comparable. The patient response based on endocrinological pharmacotherapeutic compliance showed that among 100 new type II diabetes mellitus patients, of early moderate grade, receiving metformin or sitagliptin monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, for 3 months, all the patients had completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients. The prescription rates of different anti-diabetic drugs in percentages showed that metformin was most commonly prescribed (75 prescriptions, 75%), followed by sitagliptin (25 prescriptions, 25%). The prescription rates of anti-diabetic drugs were as follows: metformin>sitagliptin. The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were found in 100% of prescriptions. The correlated molecular pharmacological analysis established an appropriate and adequate clinical pharmacotherapeutic application of metformin and sitagliptin among type II diabetic patients, based on the analytical evidence-based deductions regarding the systematic structural and organisational synchrony in the endocrinological pharmacodynamic and pharmacotherapeutic response mechanisms of metformin and sitagliptin, which were significantly effective in the comprehensive anti-diabetic treatment. The monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy of metformin or sitagliptin, was observed to be quite efficacious, which had controlled type II diabetes mellitus among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, in the successive 3 months. The adverse effects observed with monotherapy, or combination therapies, or mixed regimen of monotherapy and combination therapy, were statistically nonsignificant. Therefore, the monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, were safe and tolerable. The patients were satisfied with the anti-diabetic tertiary medical healthcare provided.

From a similar study, it was obtained that the demographic characteristics of the patients were comparable. Metformin was most commonly prescribed (120 prescriptions, 80%) followed by sitagliptin (21 prescriptions, 14%) and remogliflozin (9 prescriptions, 6%). The prescription rates of antidiabetic drugs were as follows: metformin>sitagliptin>remogliflozin. The monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy of metformin, sitagliptin, or gemigliptin, was observed to be quite efficacious, which had controlled T2DM among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, in the successive 3 months. The adverse effects observed with monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, were statistically non-significant. Therefore, the monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, was safe and tolerable.

In another study, among 150 new type II diabetes mellitus patients, of early moderate grade, receiving metformin monotherapy for 1 month, 50 uncontrolled diabetic patients, who had achieved adequate glycaemic

control with metformin monotherapy, or who were lost to follow-up, or who had dropped out due to adverse effects, or who had withdrawn voluntarily, were excluded from the study. The remaining 100 patients, received remogliflozin and metformin combination therapy, for 15 days. These patients had completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients. The demographic characteristics of the patients were comparable. The monotherapy of metformin and the combination therapy of remogliflozin and metformin were observed to be safe, which had controlled type II diabetes mellitus among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, in 1.5 months. There were no adverse effects observed with the monotherapy of metformin as well as the combination therapy of remogliflozin and metformin, which were statistically non-significant. The monotherapy of metformin and the combination therapy of remogliflozin and metformin were observed to be safe and tolerable.

In yet another study, the demographic characteristics of the patients were comparable. Metformin was most commonly prescribed (80 prescriptions, 80%), followed by sitagliptin (16 prescriptions, 16%), and gemigliptin (4 prescriptions, 4%). The prescription rates of anti-diabetic drugs were as follows: metformin>sitagliptin>gemigliptin. The monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy of metformin, sitagliptin or gemigliptin, was observed to be quite efficacious, which had controlled type II diabetes mellitus among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, in the successive 3 months. The adverse effects observed with monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, was statistically non-significant. Therefore, the monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, were safe and tolerable.

The demographic characteristics of the patients were comparable. 100 new type II diabetes mellitus patients, of early moderate grade, receiving metformin or sitagliptin monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, for 3 months, all the patients had completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients. Metformin was most commonly prescribed (75 prescriptions, 75%), followed by sitagliptin (25 prescriptions, 25%). The prescription rates of anti-diabetic drugs were as follows: metformin>sitagliptin. The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were found in 100% of prescriptions. The monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy of metformin or sitagliptin, was observed to be quite efficacious, which had controlled type II diabetes mellitus among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, in the successive 3 months. The adverse effects observed with monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, was statistically non-significant. Therefore, the monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, were safe and tolerable. All the global patients were satisfied with the different attributes of anti-diabetic tertiary medical healthcare provided, like immediate treatment delivery,

appropriate convenient investigations and treatment, quickly controlled diabetes, safe and tolerable treatment, early accessible medications, convenient administration of medications and maintenance of symptom-free controlled diabetic period.

On comparative analysis with yet another similar study on the glycaemic efficacy and safety of sitagliptin initiation during metformin dose-escalation within type II diabetic patients not at glycated haemoglobin levels on sub-maximal metformin doses, it was found that there was improvement in the glycaemic response and HbA1c levels, with similar safety and tolerability, compared to metformin monotherapy.

Even in the treatment of gestational diabetes mellitus, along with the American Diabetes Association recommended first-line therapy with insulin, metformin is also widely prescribed pharmacotherapeutically. The American College of Obstetricians and Gynaecologists and the National Institute for Health and Care Excellence in the United Kingdom recommends that either insulin or metformin can be prescribed as a first-line pharmacotherapeutic option for gestational diabetes mellitus[1-4].

Thus, this systematic review and meta-analysis had the merits that the reviewing was done with a well-organised methodology, along with thorough explanations and analyses of the medical study literature and evidence, compiled from the numerous studies conducted, which authenticated the research question of this systematic review and meta-analysis, regarding the oral hypoglycaemic rational pharmacotherapeutic applications of metformin. There were not many limitations in this study, worth a significant mention.

Therefore, this systematic review and meta-analysis provided the refined qualitatively synthesised medical records, study literature and databases on oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy, with well-comprehensible elaborations and interpretations, which is certainly a comprehensive progress towards future innovations in more effective anti-diabetic pharmacotherapy.

Conclusion:

Therefore, this systematic review and meta-analysis, contributed 2140 refined and relevant medical records, among total 2876 initial records, obtained from the study databases search. It also qualitatively described and comparatively analysed the oral hypoglycaemic rational pharmacotherapeutic research on metformin monotherapy and combination therapy, which comprehensively explained this systematic review and meta-analysis.

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Declarations:

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