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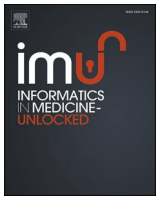

Minimization of drug interactions in polypharmacy treatments of diabetes mellitus type 2 with cardiovascular comorbidities by using the decision support tool PM-TOM

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ABSTRACT

Background: Combined polypharmacy treatments of multi-diseases like diabetes mellitus type 2 (DMT2) with its comorbidities could lead to serious adverse reactions (ADR) due to drug-drug interactions (DDIs). This study aimed to demonstrate that these DDI ADRs can be significantly reduced by carefully examining DDIs of recommended drugs and using advanced clinical decision support (CDS) tools, like PM-TOM (Personal Medicine: Therapy Optimization Method).

Method: DMT2 with heart failure (HF) and atherosclerotic cardiovascular disease (ASCVD) were taken for analysis. First, 20 drug classes were selected, recommended in relevant medical guidelines (US, European and Canadian); for example, biguanides, sodium-glucose transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, insulins, angiotensin 2 receptor blockers, angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, diuretics, and statins. Next, these classes were combined into polypharmacy treatment cases, which were organized into three groups: Basic (combinations of three drug classes), Medial (five), and Advanced (eight). Then, the tool PM-TOM was used to find treatments with minimal and maximal drug interactions (MIN-DDI and MAX-DDI) for each case. Finally, these two treatments' minimal, average and maximal DDIs were calculated and statistically analyzed to examine the scope and effects of optimizing polypharmacy treatments in each case group.

Results: In the Basic group, 16 polypharmacy treatment cases were created; in the Medial 210 and the Advanced 736. The MIN-DDI and MAX-DDI treatments in each case group showed significant DDI differences; for example, in the Basic group, the average DDI count in the MIN-DDI treatments was 0.19 and in the MAX-DDI ones 1.75, while in the Medial and Advanced groups, these indicators were 1.66 and 7.66, and 5.76 and 20.52, respectively. Also, 87% of optimized treatments (MIN-DDI) in the Basic group showed no DDIs, 37% in the Medial, and 9% in the Advanced. In addition, 70% of cases in the Medial group had at most two DDIs, and 49% in the Advanced group at most five.

Conclusions: These findings suggest that DDI ADRs in randomly selected (unoptimized) DMT2 polypharmacy treatments can be substantially reduced using specialized decision support tools, increasing patients' chances for successful treatment and decreasing health care costs. Similar findings can be expected for other multi-diseases as well.

1. Introduction

1.1. Drug-drug interactions and adverse drug reactions

Adverse drug reactions (ADRs) in polypharmacy treatments, due to drug-drug interactions (DDIs) or other reasons, can cause complex medical conditions and even death in patients exhausted by illness, inadequate treatment, or age-related issues and, in addition, increase healthcare costs. The article *Preventable Adverse Drug Reactions: A Focus on Drug Interactions* by US Food & Drug Administration Agency (FDA) [1] summarizes alarming findings from various studies, such as that ADRs could be the fourth leading cause of death in the US. Also, ADR

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costs could be as high as 136 billion yearly (data from 2000), and ADR rates increase exponentially after a patient is on four or more medications. A newer study [2] announced even more serious findings: the estimated annual cost of drug-related morbidity and mortality from nonoptimized medication therapy in 2016 was $528.4 billion, equivalent to 16% of US healthcare expenditures. The above FDA report concludes that ADRs are a significant public health problem that is, for the most part, preventable.

Clinical decision support (CDS) tools, currently used in clinical practice [3], raise alerts on DDIs in prescribed medication treatments without suggesting how to minimize them. The alert numbers can be high, so doctors override them without changing the prescribed treatments. For example, a study [4] collected data on DDI alerts and override reasons from 10 clinical sites across the United States and found that the overall override rate was very high, at 91%, where 78% of these overrides states: *will monitor or take precautions*, *not clinically significant*, and the *benefit outweighs the risk*. This phenomenon is called *Alert fatigue,* where too many alerts are presented so that health providers dismiss them regardless of their importance. One of the main reasons for alert fatigue is the high number of alternative polypharmacy treatments, so doctors (physicians, clinicians, or clinical pharmacists) cannot optimize them without specialized CDS tools.

1.2. Study motivation and objectives

Adding polypharmacy optimization functions to CDS systems would decrease alert fatigue and enable doctors to focus on finding effective and stable polypharmacy treatments that do not need frequent adjustments caused by DDIs. Consequently, the mortality and morbidity of polypharmacy patients would be reduced, their chances for recovery would increase, and overall healthcare costs would decrease.

This study aims to demonstrate the benefits of using such a tool, called PM-TOM (Personalized Medicine: Therapy Optimization Method) [5], on the example of polypharmacy treatments of diabetes mellitus type 2 (DMT2) with its cardiovascular comorbidities.

The specific objectives of this study were to

1. Demonstrate, on the example of a complex multi-disease, that numerous alternative polypharmacy treatments exist with substantially different DDIs and, consequently, ADRs.
2. Show that the polypharmacy optimization tools can find treatments with significantly reduced counts of DDIs and their ADRs.
3. Prove that these tools can find optimized polypharmacy treatments efficiently, which is a key requirement to enable effective teamwork of doctors involved in the patient's care.

1.3. Why diabetes mellitus type 2 and cardiovascular diseases?

DMT2 is a multi-disease of high health significance and widespread occurrence, particularly in older populations. Its medication treatments are usually complicated by several comorbidities, such as various forms of cardiovascular diseases (CVD), chronic kidney disease (CKD), obesity, and hypercholesterolemia (HC). For example, a study [6] found that diabetic patients had more comorbidities (10.35 vs. 7.48 in the control group) and received more drugs (7.81 vs. 5.33) than their non-diabetic counterparts. In addition, the mean number of DDIs and drug-food interactions (DFIs) was higher in polypharmacy treatments of DMT2 patients vs. controls: 8.86 vs. 4.98.

According to World Health Organization [7], adults with diabetes historically have a two or three-times higher rate of CVD than adults without diabetes. In addition, a study [8] provides a systematic review of scientific evidence about the prevalence of CVD in DMT2 patients across the world from 2007 to 2017 and found that CVD affected 32.2% of cases, 29.1% had atherosclerosis, 21.2% coronary disease, and 14.9% heart failure. In addition, CVD was found to cause death in 9.9% of cases.

This study is focused on DMT2 with its frequent CVD comorbidities of heart failure (HF) and atherosclerotic cardiovascular disease (ASCVD). The treatments of this multi-disease are covered in detail in the DMT2 and CVD medical guidelines, for example, US [9–11], European [12–14], and Canadian [15–17]. In addition, recommendations for the treatment and prevention of dyslipidemia as a possible precursor of ASCVD are also elaborated in numerous papers, for example, [18–20]. All these publications provide detailed recommendations about drug classes to be used or avoided in different stages of DMT2 with these comorbidities. However, these guidelines did not elaborate on the DDI ADR risks in these regimens. Therefore, this study aimed to address this deficiency as well.

1.4. Why PM-TOM?

PM-TOM [5] is a polypharmacy optimization tool that finds treatments with minimized drug-drug, drug-condition, and drug-gene interactions (DDIs, DCIs, and DGIs). It takes as inputs a patient's conditions, genome (optional), and candidate drugs (or drug classes), which the doctor defines after considering the patient's conditions, test results, allergies, age, and ADRs. In addition, the doctor can indicate preferred drugs for each condition, which will form the Initial Treatment (IT) [5]. When the IT is not defined, the tool will form it as a combination of single drugs, one from each candidate drug set, having a minimal count of interactions with all drugs.

PM-TOM applies a heuristic algorithm that starts from the IT and then improves it by replacing each IT drug with a candidate drug for the same condition but with minimal DDIs, DCIs and DGIs against other IT drugs [5]. In that way, the algorithm is investigating only a subset of all possible alternative treatments rather than all possible ones. For example, if the doctor has selected k classes, each with M_i drugs, $i=1 \ldots k$, and the IT is composed of a single drug from each selected class, then the tool would investigate $M_1 + M_2 + \ldots + M_k$ alternative treatments rather than $M_1 * M_2 * \ldots * M_k$. As the tool investigates only a subset of candidate treatments, it can achieve high efficiency. Although the tool does not necessarily find the polypharmacy treatments with the absolute minimum count of DDIs, it still finds one close to it.

PM-TOM was developed and tested using the electronic medical records of the Harvard Personal Genome Project (PGP) [21]. Studies [5,22,23] demonstrated that the tool could suggest significantly improved treatments while using the doctor's expertise and meeting the efficiency criteria. Thus far, to the author's best knowledge, tools with similar functionality have not been introduced yet.

2. Method

Fig. 1 shows the study steps. In the first step, the DMT2 comorbidities HF and ASCVD were chosen for analysis. The same method can be applied to other multi-diseases as well.

In Step 2, 20 recommended drug classes for treating these diseases were selected (Table 1) according to the above medical guidelines. As a result, the following eight classes were chosen for the treatment of DMT2: biguanides-metformin (BG), sodium-glucose transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1ra), sulfonylureas (SU), dipeptidyl peptidase 4 inhibitors (DDP4i), and the rapid-, intermediate- and long-acting insulins (INS-R, INS-I, INS-L). This study's class INS-I includes insulin human and its variant neutral protamine Hagedorn (NPH) insulin, frequently classified as fast-acting and intermediate-acting insulins, respectively. However, as they have the same protein formula, drug ingredient ID, and DDIs, they were classified into the same class. For HF, seven classes of drugs were included: aldosterone receptor antagonists (MRA), angiotensin 2 receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEi), beta-adrenergic blockers (BB), loop diuretics (LD), potassium-sparing diuretics (PSD), and thiazide diuretics (TD); and five for ASCVD: statins (STAT), cholesterol absorption inhibitors-ezetimibe (CAI), fibric acid

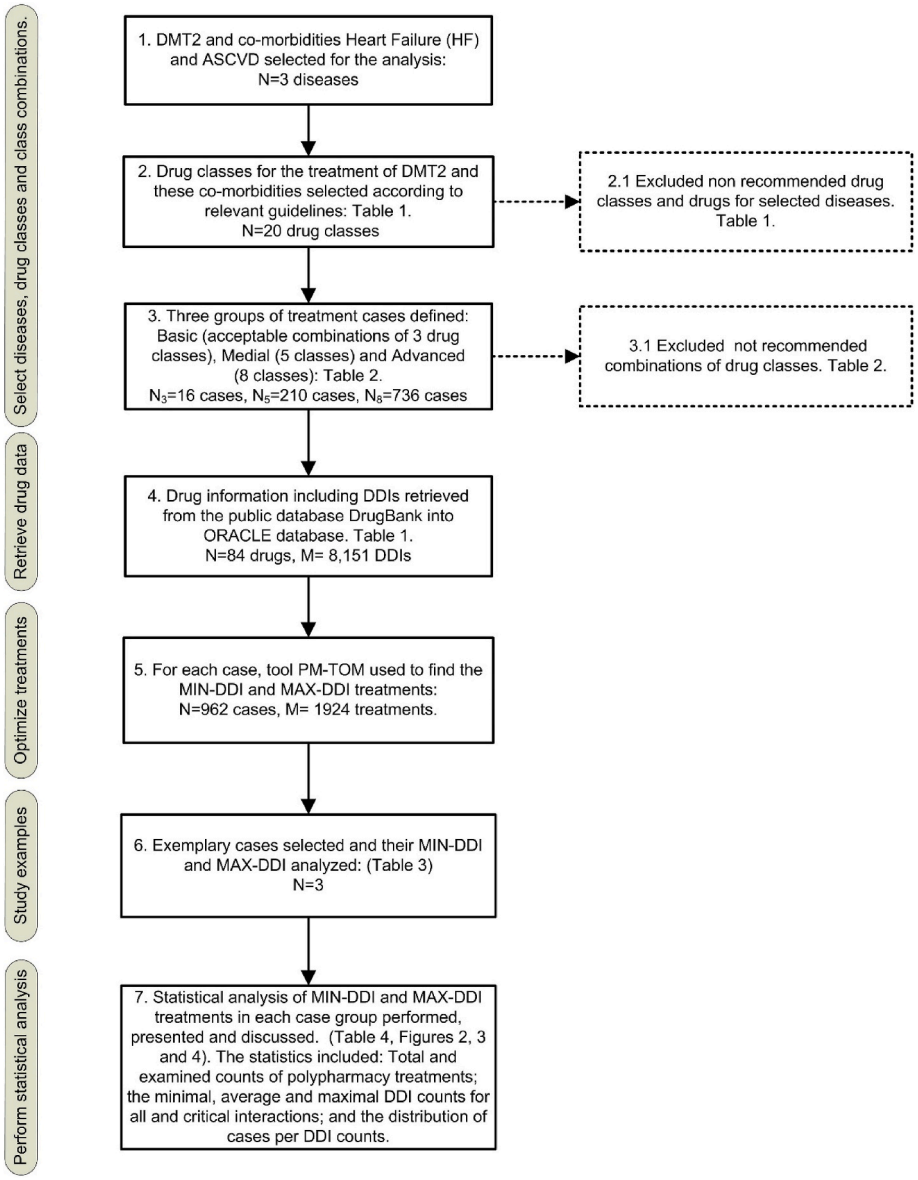

Fig. 1. The study steps. Selection of a multi-disease, finding applicable drug classes, and defining treatment case groups. Data preparation. Finding treatments with minimal and maximal DDIs. Analysis of exemplary cases. Statistical Analysis.

agents (FAA), proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), and bile acid sequestrants (BAS).

In Step 2.1, drugs and drug classes not recommended for the treatment of DMT2 and HF were excluded from the analysis, such as thiazolidinediones (TZD) [10,14,17], calcium channel blockers (CCB) [13,17], and the DDP4i drugs saxagliptin and alogliptin [10,17,24]. Some studies, like [25], report that some of these drugs may not pose a much higher risk than other antihyperglycemic agents; however, further discussion of these differences is not in this study's scope. Also, other drug classes used to treat these conditions, for example, alpha-glucosidase inhibitors, meglitinide, anti-obesity agents, and dopamine agonists, were not included, as they were not elaborated on in these guidelines.

The treatment cases for analysis and their groupings were introduced in step 3. A treatment case (referred to as a case) is an acceptable combination of drug classes for the polypharmacy treatment or prevention of the observed multi-disease. The cases with the same number of drug classes were organized into case groups: Basic (one drug class for DMT2, HF and ASCVD each), Medial (combinations of two drug classes for DMT2, two for HF and one for ASCVD) and Advanced (combinations of three drug classes for DMT2, three for HF and two for ASCVD). These groups are specified in Table 2.

Unrecommended drug class combinations are identified in Step 3.1. For example, the following class combinations were excluded from the above cases: SGLT2i and insulins due to increased drug-related adverse events, urinary tract infections, and genital infections [26], GLP-1ra and DPP4i due to pancreatitis risk [27], SU and insulins due to increased mortality [28]. Some of these drug class combinations classes may be justified in clinical practice; however, they were excluded to keep this study focused on accepted polypharmacy treatments of selected diseases.

While the case groups could also correspond to the progression stages of DMT2 with observed comorbidities, they did not intend to suggest nor exclude any possible polypharmacy treatment of these diseases.

In step 4, information about 84 drugs from the above classes was extracted from DrugBank [29], including their classes, uses, and DDIs, and loaded into the ORACLE database. Experimental or withdrawn drugs were excluded. Table 1 shows the drugs selected in each class. A

Table 1
Selected drug classes and drugs to study the DMT2, HF, and ASCVD treatments. Excluded classes and drugs: saxagliptin and alogliptin (DDP4i), thiazolidinediones (TZD), and calcium channel blockers (CCB).

Drug Class	Class Acronym	Disease Acronyms	Drug ct.	Drugs
Aldosterone receptor Antagonists	MRA	HF	2	Eplerenone, spironolactone.
Angiotensin 2 receptor blockers	ARB	HF	7	Candesartan, candesartan cilexetil, irbesartan, losartan, olmesartan, telmisartan, valsartan.
Angiotensin-converting enzyme inhibitors	ACEi	HF	11	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril, zofenopril.
Beta-adrenergic blockers	BB	HF	5	Atenolol, bisoprolol, carvedilol, metoprolol, nebivolol.
Biguanides	BG	DMT2	1	Metformin.
Bile acid sequestrants	BAS	ASCVD	3	Cholestyramine, colesevelam, colestipol.
Cholesterol absorption inhibitors	CAI	ASCVD	1	Ezetimibe.
Dipeptidyl peptidase 4 inhibitors	DDP4i	DMT2	3	Anagliptin, linagliptin, vildagliptin.
Fibric acid agents	FAA	ASCVD	4	Bezafibrate, clofibrate, fenofibrate, Ggmfibrozil.
GLP-1 receptor agonists	GLP-1ra	DMT2	6	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide.
Insulin regular and immediate-acting	INS-I	DMT2	1	Insulin regular/insulin NPH (these insulins have the same protein formula but different acting times).
Insulin long-acting	INS-L	DMT2	3	Insulin degludec, insulin detemir, insulin glargine.
Insulin rapid-acting	INS-R	DMT2	3	Insulin aspart, insulin glulisine, insulin lispro.
Loop diuretics	LD	HF	5	Bumetanide, etacrynic acid, furosemide, piretanide, torasemide.
PCSK9 inhibitors	PCSK9i	ASCVD	2	Alirocumab, evolocumab.
Potassium-sparing diuretics	PSD	HF	4	Amiloride, eplerenone, spironolactone, triamterene.
Sodium-glucose transporter 2 inhibitors	SGLT2i	DMT2	4	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin.
Statins	STAT	ASCVD	7	Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin.
Sulfonylureas	SU	DMT2	7	Chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, gliclazide.
Thiazide diuretics	TD	HF	5	Chlorothiazide, chlorthalidone, indapamide, hydrochlorothiazide, trichlormethiazide.
20			**84**	

total of 8,151 DDIs between these drugs were found.

In Step 5, the PM-TOM tool was applied to each case to find the drug combinations with minimal and maximal drug interactions (MIN-DDI and MAX-DDI). The IT for finding a MIN-DDI was formed as a combination of drugs from the case classes with minimal DDIs against all other study's drugs (Table 1). On the other hand, for the MAX-DDI treatments, the drugs with maximal interactions were used. As the outcome of this step, PM-TOM generated MIN-DDI and MAX-DDI for all 962 cases. Examples of the MIN-DDI and MAX-DDI treatments are shown in Table 3. The tool was implemented in the cloud versions of the ORACLE applications server (APEX), version 22, and the ORACLE database, version 21.

Table 2
Treatment case groups, drug classes, and exclusions. The treatments in these groups could correspond to the stages of DMT2 with the selected comorbidities.

Case group	Drug combinations				
	Classes	DMT2	HF	ASCVD	Exclusions
Basic	3	One drug from any DMT2 class	One ACEi or ARB drug	One STAT drug	
Medial	5	Two drugs, each from two different DMT2 classes	One ACEi or ARB drug + One BB, MRA, LD, TD, or PSD drug	One STAT drug	Drug combinations of SU and any INS, GLP-1ra and DPP4i, SGLT2i and any INS.
Advanced	8	Three drugs, each from three different DMT2 classes	One ACEi or ARB drug + One BB drug + One MRA, LD, TD, or PSD drug	One STAT drug + One BAS, CAI, FAA, or PCSK9i drug	Drug combinations of SU and any INS, GLP-1ra and DPP4i, SGLT2i and any INS.

In step 6, one representative case from each group was selected to illustrate the study results. Table 3 shows their drug classes, MIN-DDI and MAX-DDI treatments, and detailed descriptions of their critical and other DDIs.

Next, in Step 7, the DDI statistics of the MIN-DDI and MAX-DDI treatments for each case group were calculated. The statistical results presented in Table 4 and Fig. 3 include the minimal, average, and maximal DDI counts for each case group and treatment type (MIN-DDI and MAX-DDI). In addition, the distribution of cases per DDI count was presented for MIN-DDI treatments in Fig. 3 and MAX-DDI ones in Fig. 4. Finally, the examples and statistical results are analyzed in Section 3 and discussed in Section 4, particularly how they meet the study objectives.

The complete results of the study can be found at site [34], including cases in each group, drug combinations for each MIN-DDI and MAX-DDI, their DDIs, and the complete statistical results.

3. Results

3.1. Sample cases

Table 3 illustrates the MIN-DDI and MAX-DDI treatments for select cases from each group. Each case is explained in terms of considered drug classes, drugs selected in each treatment type, their DDI counts (all and critical DDIs), and the DDI details. These cases were defined as follows. Classes BG (metformin) for DMT2, ARB for HF, and STAT for ASCVD were included in all cases, and GLP-1ra for DMT2 and BB for HF were added in the Medial and Advanced cases. Finally, class INS-L was added for DMT2, LD for HF, and CAI (ezetimibe) for ASCVD in the Advanced stage.

After applying PM-TOM to all three cases, MIN-DDI treatment in the Basic case showed only one non-critical DDI, one critical and two non-

Table 3
Examples of the MIN-DDI and MAX-DDI treatments for selected cases. The range of DDI counts in MIN-DDI and MAX-DDI is (1,2) in the Basic case, (3, 7) in the Medial, and (8, 20) in the Advanced, indicating a large room for minimization of DDI ADRs in nonoptimized treatments.

Case group	Treatment.	DMT2	HF	ASCVD	DDI ct.	Critical	DDI Descriptions
Basic (BG, ARB, STAT)	**MIN-DDI**	BG: metformin	ARB: candesartan cilexetil	STAT: pitavastatin	1	0	1. Metformin may increase the hypolipidemic activities of pitavastatin.
	MAX-DDI	BG: metformin	ARB: valsartan	STAT: pravastatin	2	0	1. The excretion of valsartan can be decreased when combined with pravastatin.2. Metformin may increase the hypolipidemic activities of pravastatin.
Medial (BG, GLP-1ra, ARB, BB, STAT)	**MIN-DDI**	BG: metformin GLP-1ra: dulaglutide	ARB: candesartan cilexetil BB: bisoprolol	STAT: pitavastatin	3	1	1. Metformin may increase the hypolipidemic activities of pitavastatin. 2. Metformin may decrease the excretion rate of bisoprolol, which could result in a higher serum level. 3. The risk or severity of hypoglycemia can be increased when metformin is combined with dulaglutide.
	MAX-DDI	BG: metformin GLP-1ra: Lixisenatide	ARB: valsartan BB: metoprolol	STAT: pravastatin	7	2	1. The risk or severity of hypoglycemia can be increased when metformin is combined with lixisenatide. 2. Metoprolol may decrease the excretion rate of lixisenatide, which could result in a higher serum level. 3. The serum concentration of metformin can be increased when combined with metoprolol. 4. Metformin may increase the hypolipidemic activities of pravastatin. 5. The serum concentration of metoprolol can be increased when combined with pravastatin. 6. The excretion of valsartan can be decreased when combined with pravastatin. 7. The risk or severity of hyperkalemia can be increased when valsartan is combined with metoprolol.
Advanced (BG, GLP-1ra, INS-L, ARB, BB, LD, STAT, CAI)	**MIN-DDI**	BG: metformin GLP-1ra: dulaglutide INS-L: insulin detemir	ARB: candesartan cilexetil BB: bisoprolol LD: piretanide	STAT: pitavastatin CAI: ezetimibe	8	2	1. The metabolism of bisoprolol can be decreased when combined with ezetimibe. 2. Ezetimibe may decrease the excretion rate of pitavastatin, which could result in a higher serum level. 3. The risk or severity of hypoglycemia can be increased when metformin is combined with dulaglutide. 4. Metformin may decrease the excretion rate of bisoprolol, which could result in a higher serum level. 5. The risk or severity of hypoglycemia can be increased when metformin is combined with insulin detemir. 6. The therapeutic efficacy of metformin can be increased when combined with piretanide. 7. Metformin may increase the hypolipidemic activities of pitavastatin. 8. The serum concentration of ezetimibe can be increased when combined with candesartan cilexetil.
	MAX-DDI	BG: metformin GLP-1ra: exenatide INS-L: insulin glargine	ARB: valsartan BB: metoprolol LD: torasemide	STAT: rosuvastatin CAI: ezetimibe	20	4	1 Ezetimibe may decrease the excretion rate of rosuvastatin, which could result in a higher serum level. 2. Exenatide may increase the hypoglycemic activities of insulin glargine. 3. The risk or severity of hypoglycemia can be increased when insulin glargine is combined with metformin. 4. Metoprolol may increase the hypoglycemic activities of insulin glargine. 5. The therapeutic efficacy of insulin glargine can be increased when combined with rosuvastatin. 6. The therapeutic efficacy of insulin glargine can be increased when combined with torasemide. 7. The risk or severity of hypoglycemia can be increased when metformin is combined with exenatide. 8. Metformin may increase the hypolipidemic activities of rosuvastatin. 9. The serum concentration of ezetimibe can be increased when combined with metoprolol. 10. The serum concentration of metformin can be increased when combined with metoprolol. 11. The metabolism of metoprolol can be decreased when combined with rosuvastatin. 12. The therapeutic efficacy of exenatide can be increased when combined with rosuvastatin. 13. The therapeutic efficacy of exenatide can be increased when combined with torasemide. 14. The therapeutic efficacy of metformin can be increased when combined with torasemide. 15. The risk or severity of adverse effects can be increased when torasemide is combined with metoprolol. 16. The metabolism of rosuvastatin can be decreased when combined with torasemide. 17. The excretion of ezetimibe can be decreased when combined with valsartan.18. The risk or severity of hyperkalemia can be increased when valsartan is combined with metoprolol.19. The metabolism of rosuvastatin can be decreased when combined with valsartan. 20. The metabolism of torasemide can be decreased when combined with valsartan.

critical DDIs were found in the Medial case, and two critical and six non-critical in the Advanced. On the other hand, the corresponding MAX-DDI treatments displayed significantly higher counts of the critical and other DDIs: no critical and two non-critical in the Basic case, two critical and five non-critical in the Medial, and four critical and 16 non-critical in the Advanced.

The first observation regarding the selected medication is that candesartan cilexetil (ARB), and pitavastatin (STAT) were selected in all MIN-DDI treatments, in addition to metformin (BG), as the only choice in its class. These drugs have minimal interactions and other benefits, as found in several studies. For example, a study [30] indicates that candesartan cilexetil significantly reduced the incidence of cardiovascular death, hospital admissions for decompensated heart failure, and all-cause mortality in chronic heart failure patients. Also, the selection of pitavastatin is aligned with the study [31], which suggests that this medication has beneficial effects on the cardiometabolic lipid profile and a low potential for drug-drug interactions. In addition, another study [32] reported that pitavastatin reduced the risk of new-onset DMT2 compared with atorvastatin or rosuvastatin.

Second, dulaglutide (GLP-1ra) and bisoprolol (BB) were selected in the Medial and Advanced cases. This result is aligned with the diabetes pharmacotherapy guidelines [11], which recommend dulaglutide as the first choice among GLP-1ra drugs with FDA-approved CVD benefits. Also, bisoprolol was compared in the study [33] with carvedilol, another frequently used BB, with the conclusion that bisoprolol induced demonstrable improvement in pulmonary function and caused fewer adverse events.

Third, insulin detemir (INS-L), piretanide (LD), and ezetimibe (CAI) were added to the above drugs in the Advanced case. As expected, the combinations of three DMT2 drugs, three HF drugs, and two ASCVD could have several DDIs (8 in this case). However, other drug combinations would have higher or the same DDI counts in this case.

In the MAX-DDI treatments, valsartan (ARB) was found in all cases, metoprolol (BB) in the Medial and Advanced cases, and pravastatin (STAT) in the Basic and Medial ones, indicating that these drug combinations should be avoided in the observed treatment case.

3.2. Statistical results

Statistical analysis of all results is presented in Table 4 and graphically in Fig. 2.

The first part of Table 4, labelled Treatments, shows the counts of drug classes, cases, the examined and all possible drug combinations for each case group and treatment type. The 962 considered cases can produce 61,198,200 drug combinations for each treatment type (on average, 63,616 per case), each representing a potential polypharmacy treatment of the observed diseases. On the other hand, the PM-TOM algorithm examined only 40,393 combinations, or 42 per case on average, to find a MIN-DDI or MAX-DDI.

The rest of the table presents the minimal, average and maximal counts of DDIs (all and critical) for MIN-DDI and MAX-DDI treatments in each case group, indicating the possible room for improvement of DDI counts in unoptimized polypharmacy treatment in each case group.

For example, the range of DDI counts in the MIN-DDI treatments in the Medial group is between 0 and 5, with an average of 1.66, and in the MAX-DDI treatments, between 5 and 10, with an average of 7.66. Furthermore, MIN-DDIs in the Advanced group have DDI counts between 0 and 14, with an average of 5.76, while the corresponding MAX-DDI counts are between 14 and 27, with an average of 20.52.

A particular concern is the critical DDIs, as they pose high health risks due to the possibility of severe ADRs. The range of the critical DDI counts in the Medial group MIN-DDI treatments is between 0 and 2, with an average of 0.61 and in the MAX-DDI treatments, between 0 and 4, with an average of 1.65. Also, in the Advanced group, MIN-DDIs have critical DDI counts between 0 and 6, with an average of 1.86, while these DDI counts in MAX-DDIs are between 1 and 10, with an average of 4.7.

The above statistical results are further elaborated in Figs. 3 and 4, which show the distribution of cases per each possible DDI count for each case group and treatment type. For example, 14 of 16 cases (87%) in the MIN-DDI treatments in the Basic group have no DDIs. In the Medial group, 77 out of 210 cases (37%) have no DDIs, and 148 have two DDIs or less (70%). Furthermore, 69 out of 736 cases in the Advanced group have no DDIs (9%), and 370 have 5 DDIs or less (over 49%). On the other hand, the MAX-DDI treatments show the following. In the Basic group, 10 out of 13 cases (77%) have two or more DDIs; in the Medial, 182 out of 210 cases have seven or more DDIs (87%); and in the Advanced 619 out of 736 cases have 18 or more DDIs (84%).

The ranges between the minimal and maximal DDI counts show significant room for selecting good and bad polypharmacy treatments. In addition, the percentage of optimized (MIN-DDI) treatments with no or a small number of DDIs in each case group further justifies the need and benefits of their optimization.

3.3. Tool efficiency and efficacy

Finding all 962 MIN-DDI and MAX-DDI polypharmacy treatments with PM-TOM in this study took 183 s, an average of 0.2 s per case.

This efficiency was achieved thanks to its heuristic algorithm that examines only a subset of candidate treatments. For example, to find the MIN-DDI of the case presented in Table 3 with classes BG, GLP-1ra, INS-L, ARB, BB, LD, STAT and CAI, PM-TOM spent 0.592 s examining 35 drug combinations. Finding the corresponding treatment with the (absolutely) minimal DDI count (A-MIN-DDI) required 2 min and 24 s to examine all 22,050 possible drug combinations. However, the count of possible drug combinations in the candidate polypharmacy treatments can be much higher. For example, if the doctor selected the following drug classes: GLP-1ra ($M_1 = 6$ drugs), SGLT2i ($M_2 = 4$), and SU ($M_3 = 7$) for DMT2; ACEi ($M_4 = 11$), BB ($M_5 = 5$), LD ($M_6 = 5$) for HF and STAT

Table 4
Statistical Results. The range of average DDI counts in MIN-DDI and MAX-DDI is (0.19, 1.75) in the Basic case, (1.66, 7.66) in the Medial, and (5.76, 20.52) in the Advanced. These ranges indicate scopes for minimizing DDI ADRs in nonoptimized treatments.

Treatments						DDI ct.			Critical DDI ct.		
Case group	Drug classes	Cases	Type	Examined drug combinations	All drug combinations	Minimal	Average	Maximal	Minimal	Average	Maximal
Basic	*3*	*16*	***Min-DDI***	*320*	*3,528*	*0*	*0.19*	*2*	*0*	*0.06*	*1*
			Max-DDI	*320*	*3,528*	*0*	*1.75*	*3*	*0*	*0.25*	*1*
Medial	*5*	*210*	***Min-DDI***	*6,209*	*613,872*	*0*	*1.66*	*5*	*0*	*0.61*	*2*
			Max-DDI	*6,209*	*613,872*	*5*	*7.66*	*10*	*0*	*1.65*	*4*
Advanced	*8*	*736*	***Min-DDI***	*33,864*	*60,580,800*	*0*	*5.76*	*14*	*0*	*1.87*	*6*
			Max-DDI	*33,864*	*60,580,800*	*14*	*20.52*	*27*	*1*	*4.7*	*10*
Total		*962*		*80,786*	*122,396,400*						

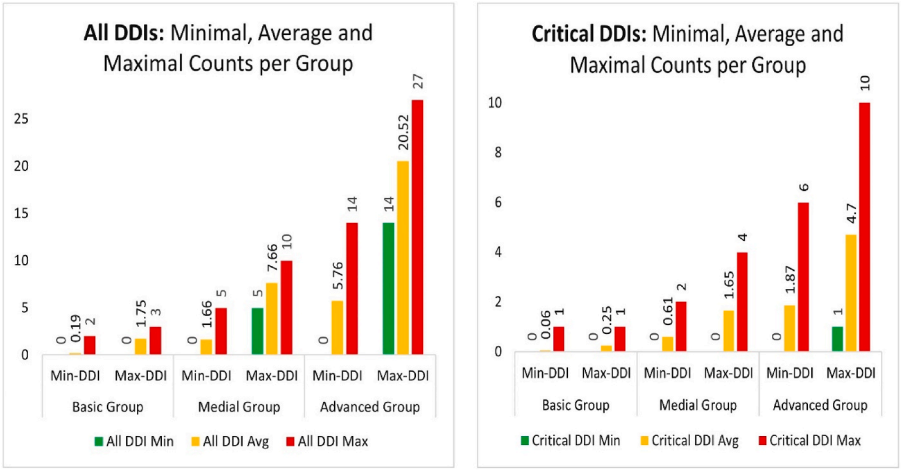

Fig. 2. The diagrams graphically illustrate the results in Table 3. The count of DDIs significantly increases with the number of drugs in the treatments. The table and the diagrams show that it is possible to find treatments in each case group with no DDIs.

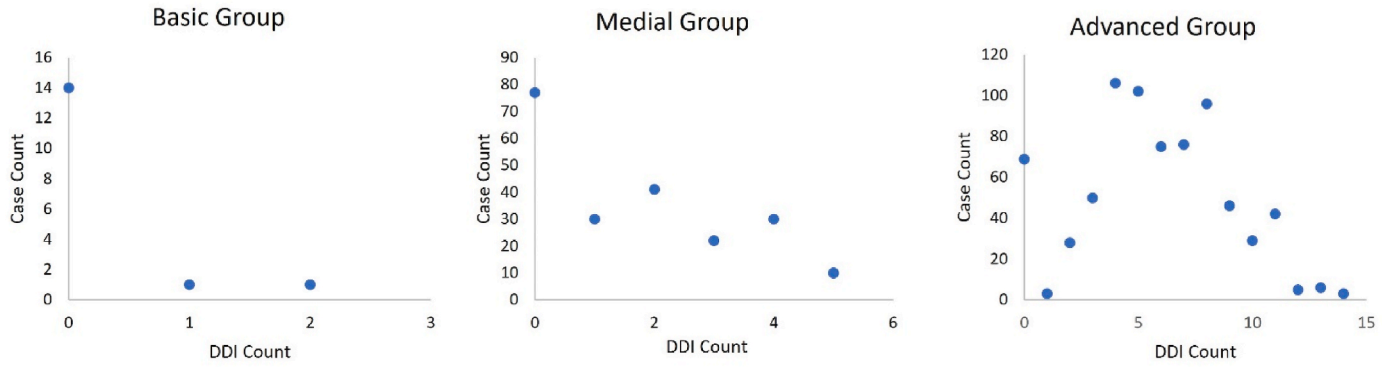

Fig. 3. Case counts per DDI count in MIN-DDI treatments. 14 of 16 cases (87%) in the Basic group, 77 out of 210 in the Medial (37%), and 69 out of 736 in the Advanced (9%) have no DDIs. One hundred forty-eight cases in the Medial group have two DDIs or less (70%), and 370 in the Advanced 5 DDIs or less (over 49%). These results show that it is possible to find polypharmacy treatments with no or a low count of DDIs.

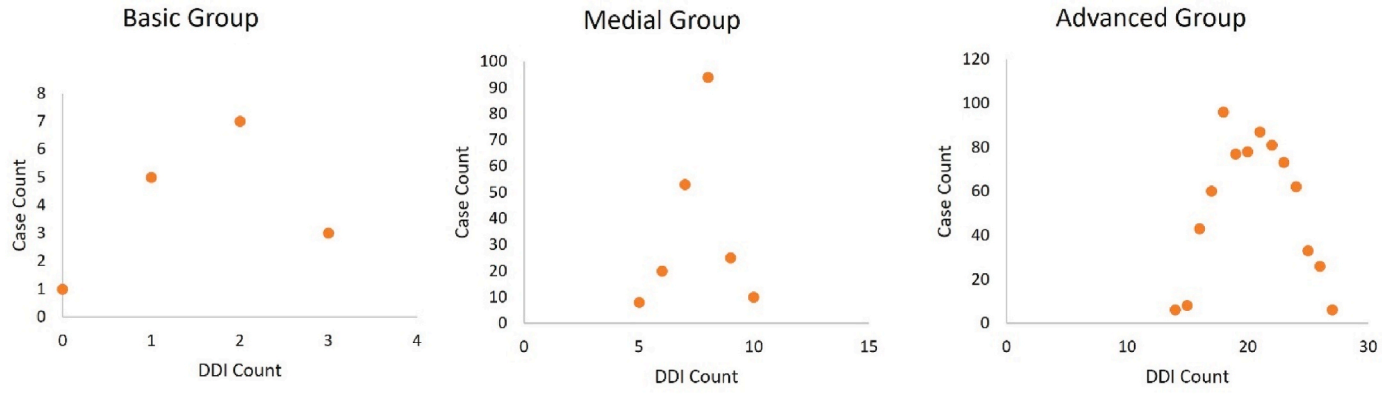

Fig. 4. Case counts per DDI count in MAX-DDI treatments. In the Basic group, 10 out of 13 cases (77%) have two or more DDIs; in the Medial, 182 out of 210 cases have seven or more DDIs (87%); and in the Advanced 619 out of 736 cases have 18 or more DDIs (84%). The ranges of DDI Counts between the corresponding MIN-DDIs and MAX-DDIs indicate that randomly selected treatments could have a high number of DDIs that require minimization.

($M_7 = 7$) and FAA ($M_8 = 4$) for ASCVD, then PM-TOM would investigate 49 combinations, rather then 1,293,600.

The polypharmacy optimization tool efficacy can be defined as the ability to find the MIN-DDI treatments with the DDI counts the same or close to the DDI counts of the corresponding A-MIN-DDI treatments.

In this study, PM-TOM efficacy was evaluated by using three testing sets: (a) the cases with no DDI in MIN-DDI treatments, (b) 10 frequently used treatment cases from the Medial group with the following structure: class 1 = BG, class 2 = DDP4i, class 3 = ACEi or ARB, class 5 = BB, LD MRA, PSD or TD and class 5 = STAT, and (c) the case with eight classes presented in Table 3, defined as a combination of eight classes: (BG, GLP-1ra, INS-L, ARB, BB, LD, STAT, CAI). The results were the

following.

(a) The percentage of MIN-DDI treatments with no DDIs was 87% in the Basic group, 37% in the Medial and 9% in the Advanced, which is identical to the DDI counts of the corresponding A-MIN-DDI treatments.
(b) A-MIN-DDI treatments from the selected testing cases showed two DDIs in three cases, three in one case, four in five cases, and five in one case. On the other hand, the corresponding MIN-DDI treatments had the same DDI count in five cases (50%), while in the other, the A-MIN-DDI treatments had one DDI less.
(c) The DDI count of MIN-DDI in the Advance case from Table 3 was eight, the same as that of A-MIN-DDI.

These examples confirm that the efficiency of the PM-TOM algorithm is rather high and that the tool efficacy is not forfeited despite the limited number of examined candidate treatments.

4. Discussion

4.1. How are the study objectives met?

Statistical results in Table 4 show that the count of polypharmacy treatments in each considered case could be very large, which might have significantly different DDI counts. For example, the Advanced group with eight drug classes has an average of 83,310 possible alternative treatments per case, with an average DDI count of 5.76 in the MIN-DDI treatments and 20.52 in the MAX-DDI ones. These results confirm that the randomly selected (unoptimized) treatments could have a high count of DDIs, which might be critical for successfully treating patients' conditions (Objective 1).

Further, these results demonstrate that optimized polypharmacy treatments (MIN-DDI) have significantly lower average DDI counts than their corresponding MAX-DDI treatments. In addition, the distribution of cases per DDI counts in Figs. 3 and 4 shows that the polypharmacy optimization can find many treatments with no or a small number of DDIs (Objective 2).

Thanks to its heuristic algorithm, PM-TOM could optimize polypharmacy treatments in this study in a sub-second time while delivering the optimal or close to optimal MIN-DDI treatments (Objective 3). The efficiency and efficacy of polypharmacy optimization tools are particularly important for the effective use of the time and expertise of medical professionals, who usually perform several administrative tasks in addition to treating patients.

4.2. Comparison with similar studies

In studies [5,22], PM-TOM was applied to depersonalized medical records provided by the participants of project PGP [21], which included patients' conditions, drugs and genomes. First, the initial treatment (IT) for each patient's condition was formed as a random selection of drugs doctors prescribed to the patient for that condition. Only one drug per condition was presumed. Then, the alternative candidate drugs were taken from the drugs from all patients' records prescribed for the same condition by the same or another doctor. Finally, the optimized treatments were found as combinations of candidate drugs with the minimal sum of the DDI and DGI counts against other IT drugs.

In contrast, this study created treatment cases from drug classes recommended in the medical guidelines, presumed that one condition can be treated with one or several drugs, and did not consider DGIs.

In the study [5], PM-TOM reduced the count of DDIs and DGIs from 22 (in IT) to 5.83 (in the optimized treatments), on average, in the group with eight conditions or more. Treatments with maximal interactions were not examined.

The study [22] focused on PGP patients with multi-diseases that include at least three frequent diseases: hypertension, diabetes mellitus, allergy, hypercholesterolemia, depression, anxiety, and asthma. In patients with eight or more conditions and at least one multi-disease, the average count of DDIs and DGIs was reduced from 24 to 9. In that study, the polypharmacy treatments with maximal counts of DDIs and DGIs were also found, and their average was 72 in the same group.

In this study, the average DDI count in minimized treatments (MIN-DDIs) having eight drugs was 5.76, and that of maximized (MAX-DDI) was 20.52. The results of all studies consistently confirm a large scope for optimizing polypharmacy treatments and the potential of PM-TOM to find optimized treatments efficiently and effectively.

To the author's knowledge, no other studies or CDS systems introduced tools and methods for minimizing drug interactions in polypharmacy treatments.

4.3. Polypharmacy optimization tool requirements

This study confirmed the benefits of adding polypharmacy optimization tools to CDS systems. These tools would naturally fit into the CDS components regarding patient safety and clinical management, elaborated, for example, in the manuscript [3].

Based on the PM-TOM experience, these tools should enable clinicians, clinical pharmacists, and physicians to

1. Select several potential drugs and drug classes for the treatment of patient's conditions based on relevant guidelines and their knowledge of treating similar cases,
2. Exclude specific individual drugs from these classes, or include drugs from other classes, if necessary,
3. Define the preferred treatment, which will be used by the tool to find drug replacements with similar effects but a lower number of DDIs,
4. Enter patients' ADRs that the tool would use to report drugs in the current treatment that may cause them,
5. Direct the tools to find treatments with minimal or nearly minimal DDIs, and optionally, DCIs, DGIs, drug-supplement interactions (DSI), and drug-food interactions (DFI),
6. Retrieve the patient's medical record (including ADRs) and its history,
7. Retrieve detailed information about drugs, interactions, products, and adverse drug effects.
8. Perform all functions effectively and efficiently.

Other useful functions of these tools would be providing drug recommendations according to patients' diagnostic tests and demographic data, drug cost limitations, and experience from treatments of similar patients' cases.

4.4. Study limitations

This study did not consider drug-condition interactions (DCIs) and drug-gene interactions (DGIs), though PM-TOM supports treatment optimization with this information. The availability of well-structured information on DCIs for the considered multi-disease is limited, and the inclusion of DGIs in the study was out of its scope.

4.5. Future studies

The study method can be applied to any other set or number of DMT2 comorbidities (including hypertension, CKD, and obesity), with or without CVD. It can also be used to analyze polypharmacy treatments of other frequent chronic diseases, such as arthritis, asthma, chronic obstructive pulmonary disease, depression and anxiety, and their combinations with the above. Future studies on polypharmacy optimization can also consider the patient's age, genotype, tests and demographic data, rules from the guidelines, rules derived from clinical expertise, as well as DSIs and DFIs.

5. Conclusions

The results of this study demonstrate on the example of DMT2 with cardiovascular comorbidities that DDIs in polypharmacy treatments can be significantly reduced by using specialized decision support tools, like PM-TOM.

Unfortunately, the CDS systems currently used in clinical practice do not include similar tools, which would help resolve the issue of alert fatigue and enable doctors to find polypharmacy treatments adequate for specific patient conditions and aligned with relevant medical guidelines. This study demonstrated that optimizing polypharmacy treatments can be done efficiently and effectively, even for cases with many treatment options.

The cases analyzed in this study could correspond to possible development stages of the considered multi-disease; however, they do not suggest the only ways to combine drug classes for its treatment. Still, these cases cover many possible treatment alternatives, sufficient to draw the above conclusions.

The study can be used as a background for other specific studies on polypharmacy treatments and possible upgrades of the corresponding medical guidelines.

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