An-Najah National University

Faculty of Graduate Studies

Evaluation of Potential Drug-drug Interactions among Medications Prescribed in Primary Health-Care Centers for Type 2 Diabetes Mellitus Patients:

A Cross-Sectional Study From Palestine.

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الإهداء

الحمد لله حمدا كثيرا طيبا مباركا فيه، علم بالقلم ما لم نكن نعلم، والصلاة والسلام على أشرف الخلق والمرسلين سيد الأنام أجمعين سيدنا محمد وعلى اله وصحبه أجمعين.

رحلة بدأناها وبتوفيق من الله العلي القدير حققنا فيها أسمى أمانيا فالقلب يبرق الإهداء فرحا مسرورا بإنجاز عظيم تكلل بالنجاح والتوفيق.

أبي: جبل عليه أستند وقت الشدة، رجل المواقف الصعبة، سندي وفخري وتاج أزين به رأسي، أهديك يا سيدي هذا الإنجاز العظيم.

أمي: السيدة الأولى في حياتي، ملاذي في حزني وفي فرحي، سر وجودي وداعمي الأكبر، القلب الحنون أهديك هذا الإنجاز لتزدادي فخرا بي كما كنت دوما.

إخوتي و اخواتي: أشقاء العمر، ورفاق الحياة، قطعة من قلبي، هدية القدر لي، أهديكم رسالتي هذه.

زوجي وأبنائي: عائلتي الصغيرة، أجمل عطايا القدر، مهجة قلبي ونبض فؤادي، إن سئلت عن السعادة فأنتم السعادة التي تغمرني، أهديكم رسالتي هذه كما هديتموني أسمى معاني الدفء والأمان.

إلى الأيدي الخفية الداعمة والتي غيب النسيان عني ذكرها فضلكم حاضر لم يغب عني أبدا، أهديكم رسالتي هذه.

الشكر والتقدير

إن كان هناك أهل للحمد والثناء فاللهم أنت أهله أعطيت فأجزلت في عطائك، فلولا هداية منك لما أنار الحق للعالمين سبيلا ،فسبحانك اللهم خير معلم علمت بالقلم القرون الاولى اخرجت هذا العقل من ظلماته وهديته النور المبين سبيلاً.

ومن بعد شكره عز وجل فالشكر كل الشكر موصول لمن هم ورثة الأنبياء وحملة لواء العلم عاليا خفاقا أساتذتي الأكارم (إن الله وملائكته وأهل السماوات والأرض حتى النملة في جحرها وحتى الحوت ليصلون على معلم الناس الخير) فلكم مني الشكر والامتنان لجهد عظيم بذلتموه لنصل إلى عظيم ما وصلنا إليه.

إلى الداعم الأكبر في هذا الصرح العلمي العظيم ذو البصمة القوية البناءة الدكتور نصر شريم قد يعجز اللسان عن إيفائك حقك في الشكر فعظيم مجهودك كبير فلك مني كل الاحترام والتقدير.

ولا يسعني في هذا المقام الا ان اشكر دكتورتي الفاضلة الدكتورة رواء الرمحي على جهودها الحثيثة وما قدمته لي من مساعدة و توجيه يدا بيد الى جانب الدكتور نصر لإنجاز هذه الرسالة.

لا أنسى رفقة يشهد القلب أمام الله محبتهم هدف جمعنا وتوحدنا في تحقيقه بعزيمة وإصرار لولاهما لما وصلنا زميلاتي الغاليات كل الشكر والعرفان لوقفتكن دوما إلى جانبي.

والشكر موصول لكل من ساهم بإخراج هذه الرسالة إلى حيز الوجود دام عطاؤكم بحر لا ينضب.

الاقرار

انا الموقعة ادناه مقدمة الرسالة التي تحمل العنوان:

Evaluation of Potential Drug-drug Interactions among Medications Prescribed in Primary Health-Care Centers For Type 2 Diabetes Mellitus Patients:

A Cross-Sectional Study From Palestine.

أقر بأن ما اشتملت عليه الرسالة هو من نتاج جهدي الخاص، باستثناء ما تمت الإشارة إليه حيثما ورد، وأن هذه الرسالة ككل أو أي جزء منها لم يقدم من قبل لنيل أي درجة أو لقب علمي أو بحثي لدى أي مؤسسة تعليمية أو بحثية أخرى.

Declaration

The work provides in the thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: Sabrine Rafat Athammeh إسم الطالبة

Signature: التوقيع

Date: 19/10/2020 التاريخ

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List of Abbreviations

ADRs	Adverse Drug Reactions
ASA	Acetyl salicylic acid
CYP450	Cytochrome P450
DDIs	Drug-Drug Interactions
DM	Diabetes mellitus
GIT	Gastrointestinal tract
GLP-1	Glucagon Like Peptide-1
HbA1c	Glycated Hemoglobin A1c
HD	Hemodialysis
IRB	Institutional Review Boards
MATE	Multidrug and toxin extrusion antiporter
MOH	Ministry of Health
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OADs	Oral Anti-diabetic Drugs
OATPs	Organic Anion-Transporting Polypeptides
OATs	Organic Anion Transporters
OCTs	Organic Cation Transporters
OTC	Over the counter
P-gp	P-glycoprotein
PMAT	Plasma membrane monoamine transporter
SGLT2	Sodium Glucose cotransporter-2
SUs	Sulfonylureas
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TZDs	Thiazolidinediones
IDF	International Diabetes Federation

Definitions

Polypharmacy: The use of multiple medications concurrently in a single individual, a threshold of at least four to five medications commonly is accepted.

Comorbidities: the state of having more than one distinct condition, which included; disease, disorder, illnesses or health problem, in an individual at the same time.

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Abstract

Background

Nowadays, there is a global healthcare concern associated with the risk of high incidence medication errors, many of which are attributed to drug-drug interactions (DDIs). Co-morbid conditions such as; diabetes mellitus, hypertension, dyslipidemia, renal disease and peripheral artery diseases require complex therapy with multiple medications. Thus, administration of more than one medication concomitantly is a common practice to control their conditions and, for this reason, polypharmacy patients are more prone to DDIs. In our country there are no local studies concerned with the prevalence of potential DDIs among type 2 diabetes mellitus patients (T2DM), that is why the study was carried out.

Aim of the Study

The aim of this study is to evaluate the potential of DDIs among medication prescribed for T2DM patients and examine factors associated with these interactions, in primary healthcare centers.

Methods

The study is an observational survey employing a cross sectional design and encompassing all T2DM patients, whom visited the primary healthcare centers of the ministry of health (MOH) between July and September 2018. The sample size is comprised of 400 patients, all from the southern part of the West Bank; Hebron and Beitlehem. The patients were interviewed for their social demographic characteristics, their medical conditions, management and treatment by questionnaire-guided interviews. All their prescriptions of drugs were input to Lexi-Comp checker to find out the potential DDIs in their medications. Besides, the assessing the modalities of DDIs according to severity to contraindicated, major, moderate, or minor interaction.

Results

Among 400 patients, a little less than the half were over 60 years, the majority of them were female. The most common co-morbid conditions present in the diabetes mellitus (DM) patients were as follows; 77.3% had cardiovascular disease (CVD), 64.5% had dyslipidemia, and 12.0% had gout. Moreover, a total of 114 different medications were used, the most commonly prescribed medications were metformin being used by 85.5%, followed by atorvastatin 74.5%, and Acetyl salicylic acid (ASA) used by 74.0% patients. The most common interactions in 61.5 % patients were ASA with Metformin followed by Glimepiride with Metformin in 40.5 % cases. Out of participants 96% patients had at least one potential DDIs.

Overall 2627 interactions were identified, with an average of 6 interaction per prescription. According to the risk rating classification, 1.33% were A, 11.72% were B, 76.67% were C, 10.01%, and 0.27% were X risk rating. The number of potential DDIs that the patients had were also related to their age, educational level, comorbidities, number of medications prescribed and complication (p value < 0.05 for each one). However, there was no significant relationship with gender, material status or smoking (p value > 0.05).

Conclusions

The prevalence of DDIs among medications prescribed for T2DM was very common. This potentially is increasing parallel with increasing age, educational level, comorbidities, number of medications, in addition to the presence of complications. Updating data related to DDIs with good and effectively communicate among healthcare providers, especially prescribers and dispensers can play an important role in minimizing DDIs.

Key Words:

Drug-drug interaction (DDIs), diabetes mellitus (DM), polypharmacy, Prescriptions, Palestine.

Chapter One
Introduction

1. Introduction

1.1 Background of the Study

Recently, a rise in potential drug interactions has been observed due to the large number of more complex therapeutic agents discovered and marketed worldwide, polypharmacy propagation, the use of complementary medicines, and non-prescription of herbal products (Sankar Saaed Joseph Azizi, & Thomas, 2015). Several types of interactions exist: drug-drug, drug-disease, drug-food, drug-alcohol, drug-herbal products, and drug-nutritional status (MalletSpinewine, & Huang, 2007).

A DDIs is an alteration of a drug therapy's effect which leads to an increase or a decrease in the efficacy of one drug caused by the presence of another drug (Karen Baxter, 2008). Substantial risk of adverse DDIs increased within patients aged over 50 years and receiving three or more medications (GoldbergMabeeChan, & Wong, 1996). Most of them are likely to be preventable, due to their clearly pharmacologic effect and well documented DDIs in previous clinical studies and reports (Juurlink Mam daniKopp Laupacis, & Redelmeier, 2003; Pirmohamed et al., 2004).

Generally, an unintended drug reaction occurs at normal doses used for prophylaxis, diagnosis, or therapy (Raschetti et al., 1999). DDIs may necessitate dosage adjustment or other medical intervention (May & Schindler, 2016; Williams & Feely, 2002). A non-interactive alternative is a good choice if it is available, if not, more appropriate precautions should be considered (Karen Baxter, 2008).

DDIs can be categorized into two main groups : pharmacokinetic and pharmacodynamics interactions (May & Schindler, 2016). In pharmacokinetic DDIs, plasma levels of a drug may increase or decrease as a result of alteration in absorption, distribution, metabolism and/or excretion, which in turn affects the pharmacological performance of the drug when taken concomitantly with another drug (May & Schindler, 2016; Williams & Feely, 2002). As a result, there is either a rise or fall of plasma levels for one or both concomitant drugs, compared with plasma levels when taken alone (Jankel & Fitterman, 1993; May & Schindler, 2016). Most of the pharmacokinetic DDIs take place at metabolism and/or absorption levels in which hepatic metabolizing enzymes and drug transporter p-glycoprotein (P-gp) expression may be altered (May & Schindler, 2016). Whereas, pharmacodynamics DDIs change the pharmacologic efficacy of a drug, causing a synergistic or antagonistic effect. Drug plasma levels, however, remain unaltered (Williams & Feely, 2002).

Diabetes mellitus (DM) is considered one of the most important public health challenges to all nations which is diagnosed in children, adolescents and younger adults (ChenMagliano, & Zimmet, 2012). Commonly, it has multiple concomitant disorders including hypertension and dyslipidemia. Recent statistics indicate that there is a two to six times greater risk of cardiovascular death in T2DM patients compared with people without the disease (Freeman & Gross, 2012; Gaede et al., 2003). These patients are most susceptible to interference between their anti-diabetic medications and antihypertensive agents, that is, lipid lowering agents interacting with the anti-diabetic agents themselves (Zaman Huri & Chai Ling, 2013). Thus, implementation of appropriate therapeutic intervention, controlling comorbidities and disease management are considerably more complicated and increasingly challenging (Freeman & Gross, 2012).

1.1.1 Underlying factors

There are many factors which may underlie some of the susceptibility to DIs (disease determinants that affect pharmacokinetic processes of a given drug (Wilkinson, 2005), organ function, dose of drugs, age, poly pharmacy, environmental factors and genetic polymorphisms, .. etc.). These are attributed not only by differences among drugs but also by differences among individuals (SmithSeidl, & Cluff, 1966). In general however, the presence of such factors does not necessitate clinical interventions since the consequences are clinically insignificant (Karen Baxter, 2008; Katzung Btram G., 2010).

1.1.2 Pharmacokinetic interactions

Pharmacokinetics is the study of the processes by which the body absorbs, distributes , metabolizes and excretes a drug and its metabolites in the body (Wilke et al., 2007).

1.1.2.1 Absorption

More than one drug administered at the same time may influence each other's absorption (rate and /or extent) from the gastrointestinal tract (GIT) into the systemic circulation and therefore its bioavailability (Welling, 1984). A number of factors can affect either the rate or the extent of drug absorption (Katzung Btram G., 2010; Roger Walker, 2012). These factors include GIT motility, path-physiological status and mal-absorption, alteration of GIT pH, complexation mechanisms (i.e., adsorption and chelation) and, more importantly, induction or inhibition of drug transport proteins in the GIT where there are different families of drug transporter proteins (P-gp drug transporter) (DuBuske, 2005; Karen Baxter, 2008; Katzung Btram G., 2010; Roger Walker, 2012; StageBrosen, & Christensen, 2015; Welling, 1984).

1.1.2.2 Distribution

Distribution is defined as the process by which a drug undergoes reversible distribution to the extracellular fluid and / or the cells of the tissues including its site of action (Richard Finkel, 2009; Roger Walker, 2012). Several drugs and their metabolite are extensively bound to plasma

proteins. Albumin, the main one, is generally binds to acidic drugs, while α1-acid glycoprotein binds to basic drugs (Roger Walker, 2012). The mechanisms of DIs associated with drug distribution are due to displacement from tissue binding sites, and alteration in local tissue barrier (Katzung Btram G., 2010; Roger Walker, 2012). These are led by protein-binding displacement by which the concentration of free, unbound drugs (pharmacologically active) (Karen Baxter, 2008) of the displaced drug in plasma increases due to the presence of another drug binding to the same plasma protein (Roger Walker, 2012). As a result of this mechanism, the concentration of the displaced drug will increase temporarily then return back to its previous concentration, owing to a compensatory increase of metabolism and distribution. Current evidence has postulated that such interactions are improbable to cause an adverse effect, but all drugs affecting the drug distribution should be used with caution, and therapeutic drug monitoring may need to be taken into consideration (Katzung Btram G., 2010; Roger Walker, 2012).

1.1.2.3 Metabolism

Metabolism refers to the processes by which the drug undergoes biotransformation (Richard Finkel, 2009). Metabolism DIs are mediated by induction or inhibition of hepatic enzymes due to concomitant drug administration (May & Schindler, 2016). The liver is the main site of drug metabolism, in addition to other sites such as the gut, kidney, skin, and lungs (Roger Walker, 2012). Drug metabolism can be divided into two

phases: phase 1 reactions such as oxidation, hydrolysis and reduction, which generally involves the cytochrome P450 (CYP450) enzymes (Karen Baxter, 2008), and phase 2 reactions which mainly involve conjugation reactions (Roger Walker, 2012), usually producing more polar and inactive compounds (Karen Baxter, 2008).

The CYP450 isoenzyme is a very large family of heme-containing enzymes (Tanaka, 1998) in hepatocytes, comprising of 57 isoenzymes, expressed by an individual gene (Wilkinson, 2005). These metabolizing enzymes can differ between individuals, according to the variations in the genes encoding them (Tanaka, 1998), which in turn may produce an inactive enzyme, reducing their catalytic activity, or resulting in an increase in their activity (Wilkinson, 2005). The most important isoenzymes are: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 which are responsible for the majority (about 80%) of oxidative drug metabolism and account for 50% of the overall elimination of most commonly used drugs (Wilkinson, 2005). Concomitant administration of enzyme inhibitors, result in the reduction of metabolizing processes of the drug. Therefore, an increase in pharmacological effects may be observed which may be associated with a number of clinically significant consequences. However, pro-drug is a special case which first needs to be converted to active metabolite. Hence a reduction effect rather than an augmented one will be achieved as a result of the inhibition of its metabolizing enzyme. Generally, the effect of enzyme inhibition appears faster than enzyme induction (Karen Baxter, 2008; Katzung Btram G., 2010). In contrast, this inhibition

effect may disappear within two to three days after discontinuing the interacting drug, and may last longer because new metabolizing enzymes must be synthesized after being destroyed by the interacting drug (Wilkinson, 2005).

1.1.2.4 Excretion

Drugs that are renal excreted can be affected by concurrent medications influencing the urinary pH, drug transporter protein, renal blood flow and active renal tubule excretion (Roger Walker, 2012). For instance, alteration in urine pH due to administration of some drugs can certainly affect ionization of weak acids or weak bases (Karen Baxter, 2008). Besides, transporters that are involved in some DIs are the organic anion transporters (OATs), organic anion-transporting polypeptides (OATPs), organic cation transporters (OCTs) and the P-gp. P-gp is the most common transporter, which has an effect on limiting cellular uptake of the drug from blood circulation (Lin & Yamazaki, 2003). The efflux of drugs out of the cells into urine, bile and intestinal lumen, appear to have a greater impact on the extent of drug absorption (via the intestine), distribution (to the brain, testis, or placenta) and elimination (in the urine and bile) (Karen Baxter, 2008). DDIs at the level of active renal tubule excretion are considered as a double edged word, as the active transport system that will be used by the drugs competitively can be used with two borders; on the one hand, by inhibiting the renal secretion of the targeted drug (e.g., probenecid (an OAT inhibitor) with penicillin (an OAT substrate)),

therefore gaining the total therapeutic effect of penicillin. On the other hand, it may lead to DDIs of concomitant drugs binding competitively on the same active transport (e.g., methotrexate with salicylates or NSAIDs), which may increase methotrexate toxicity if taken concomitantly (Karen Baxter, 2008; Roger Walker, 2012).

1.1.3 Pharmacodynamics interactions

These kinds of drug interactions have been postulated at the site of biological activity. When two drugs are administered concomitantly, the effect of one drug or both is altered (additive, synergistic or antagonistic effect) (Roger Walker, 2012), even with the same plasma therapeutic concentration (Tanaka, 1998).

1.1.3.1 Additive or synergistic interactions

These effects are obtained when similar pharmacologic classes of drugs are administered together (Katzung Btram G., 2010; Roger Walker, 2012). Additional precautions and close monitoring should be performed, because potential harmful effects in some specific synergistic could be reported (Roger Walker, 2012).

1.1.3.2 Antagonistic interactions

Undoubtedly, when two drugs having opposing pharmacological actions at the same particular receptor are taken concomitantly (e.g., warfarin with vitamin k) (Karen Baxter, 2008), an unintended adverse effect follows.

Thus, awareness of pharmacological aspects will certainly minimize pharmacodynamics DDIs (Katzung Btram G., 2010; Roger Walker, 2012).

1.1.4 Prevalence of DDIs

Globally, newer and more complex drug have emerged and marketed currently, Adverse drug reactions (ADRs) due to DDIs can occur with widely prescribing concomitant drugs having multiple pharmacologic effects (Sankar et al., 2015), which are responsible for increasing the prevalence of morbidity and mortality (Durga & Pharm, 2007).

In recent years, DDIs have become a global health concern, researchers, health care providers, clinicians facing a real challenge to identify, find, disclose, reduce and prevent the risk of potential clinically significant DDIs.

Worldwide, vigorous efforts are being made to increase the awareness of healthcare providers pertaining clinically significant interactions to identify patients at high risk of such drug interactions and adverse events, ultimately improving patient clinical consequences and outcome.

1.1.5 Diabetes Mellitus (DM) Definition and prevalence

Diabetes Mellitus is a complicated disease of glucose metabolism, accompanied by insulin deficiency and insulin resistance (Scheen, 2010b), and manifested by high blood sugar levels over a prolonged period (RizosFilippatos, & Elisaf, 2018), which involve alterations in a number of

metabolic pathways (Freeman & Gross, 2012). Moreover, they commonly exist with various comorbidities such as hypertension, dyslipidemia and kidney disease. Estimations published by The World Health Organization (WHO) for the years of 2000 and 2030 have been announced by the International Diabetes Federation (IDF) which indicate that in 2010 DM affected approximately 385 million adults, and the prevalence is expected to increase to about 439 million adults worldwide by 2030 (ShawSicree, & Zimmet, 2010).

1.1.5.1 Classification of DM

Type 1 diabetes mellitus (T1DM): is a group of metabolic disease manifested by hyperglycemia [5]. It is caused by autoimmune destruction of the β-cells of the pancreas which lead to insulin deficiency, and normally requires daily administration of insulin ("World health organization ").

T2DM: abnormalities result in resistance to insulin action. Nearly most diabetic patients (~90%) around the world are of T2DM ("World health organization"), while one third of T2DM patients go undiagnosed, until their complications appear (Association, 2012).

Gestational diabetes: is a state of hyperglycemia first diagnosed during pregnancy through prenatal screening, where the mother has a high risk of progressing to T2DM (KimNewton, & Knopp, 2002; "World health organization ").

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia (IFG): Officially termed pre-diabetes (Association, 2012), is a transition state between normality and diabetes, with a high tendency of progressing to T2DM (Rizos et al., 2018).

1.1.5.2 Diagnosis

Two practical diagnostic tests are available: 75-g oral glucose tolerance test (OGTT), and the more preferred diagnostic test fast plasma glucose (FPG) due to its ease of use, acceptability to patients, and lower cost (Association, 2012). Appendix

Appendix A summarizes different approaches used for DM diagnosis with the diagnostic criteria.

1.1.5.3 Treatment of DM

The management of the disease usually requires a stepwise adjustment of oral pharmacological therapies in combination with lifestyle modifications, and ultimately may lead to insulin requirement [6].. If glycated hemoglobin (HbA1c) ≥ 10% combined therapy or injectable therapy with insulin should be started (Rizos et al., 2018), HbA1c between 9% - 10% dual combination therapy should be considered (Rizos et al., 2018). Controlled glycemia[1] down to 7% was the common factor correlated with reduced risk of complications in T2DM patient (MamoBekeleNigussie, & Zewudie, 2019),

[1] According to the American Diabetes Association, uncontrolled glycemia is defined (HbA1c >7% for patients <65 years and >8% for patients ≥65 years).

which considered the leading cause of morbidity and mortality in person with diabetic (Hammad et al., 2017). Hypoglycemic agents consist of a set of agents acting by different mechanisms.

✓ Biguanides, e.g. ; metformin, which is considered the drug of choice for initiation mono therapy in T2DM (American Diabetes, 2017), acts by reducing hepatic glucose production (Zaman Huri & Chai Ling, 2013).

✓ Sulfonyl ureas (SUs), e.g.; glimepiride, glyburide, glipizide. In the case of inadequate control of the hyperglycemic state, additional hypoglycemic agents should be added (Rizos et al., 2018).

✓ Rapid-acting insulin secretagogues (glinides), e.g.; Nateglinide, repaglinide. These agents stimulate insulin secretion (Levetan, 2007), through closure of adenosine triphosphate (ATP)-sensitive potassium channels at pancreatic B-cell membrane (Scheen, 2005).

✓ Thiazolidinediones (TZDs) (glitazones), e.g.; pioglitazone and rosiglitazone, which were approved in the United States in 1999 (Yki-Järvinen, 2004). TZDs enhance insulin sensitivity by increasing insulin-stimulated glucose uptake in peripheral tissues which stimulate insulin secretion (Scheen, 2005; Yki-Järvinen, 2004). These selective ligands of the nuclear transcription factor peroxisome proliferator activated receptor γ (PPARγ) (Yki-Järvinen, 2004), give a synergistic effect when co-administered with SUs and metformin (Brown, 2000).

✓ α-glycosidase inhibitors, e.g.; acarbose and miglitol, that inhibit intestinal α-glycosidase enzymes, leading to subsequent delay of digestion and absorption of intestinal carbohydrates (Gaede et al., 2003; Levetan, 2007).

✓ Dipeptidyl peptidase-4 (DPP4) inhibitors, e.g.; linagliptin, saxagliptin, sitagliptin are novel therapeutic approaches in the management of T2DM. These oral agents, inhibit the gut incretin hormone degradation. Therefore, an elevation in glucagon like peptide -1 (GLP-1) plasma levels occurs, which is associated with an increase in insulin secretion from β cells and a suppression of glucagon secretion from α cells, thereby reducing hepatic glucose production (Levetan, 2007; Scheen, 2010b).

✓ Sodium-glucose cotransporter-2 (SGLT2), e.g.; canagliflozin and dapagliflozin, which reduce blood glucose levels by inhibiting renal glucose reabsorption and increasing urinary excretion of excess glucose (Kasahara et al., 2016).

✓ GLP-1 receptor agonists, e.g.; the intestinal hormone exenatide, which stimulates insulin secretion and inhibits glucagon secretion postprandial (Levetan, 2007; Scheen, 2010b).

Table 1 displays the pharmacokinetic parameters of selected oral anti-diabetic agents.

Table 1: Pharmacokinetic properties of different oral anti-diabetic drugs (OADs) (TornioNiemiNeuvonen, & Backman, 2012)

Drug	Daily dose (mg)	Oral bioavailability	Protein binding	t½ (h)	Primary route of metabolism	Active metabolites	transporters	Main route of excretion
Biguanides								
Metformin	500-3000	55%	Very low	5	Not significant	No	OCT1-2, MATE 1-2, PMAT, P-gp	Renal (80-100% unchanged)
Sulfonylureas								
Glyburide	1.75-10.5	90%	98-99%	5-7	CYP2C9 + CYP3A4?	YES	OATP2B1, P-gp, MRP1, BCRP	Renal/bile
Gliclazide	40-320	97%	95%	10	CYP2C9	NO		Renal
Glimepiride	1-6	100%	>99%	5-8	CYP2C9	YES		Renal
Glipizide	2.5-20 (-30)	80%	>95%	2-4	CYP2C9 + CYP2C19	NO		Renal (~5% unchanged)
Meglitinide analogs								
Repaglinide	0.5-16	63%	>98%	1	CYP2C8 + (CYP3A4)	NO	OATP1B1	Bile
Nateglinide	180-640	72%	97-99%	1.5	CYP2C9 + (CYP3A4)	NO		Renal (6-16% unchanged)
Thiazolidinediones								
Pioglitazone	15-45	>80%	>99%	5-6	CYP2C8	YES		Bile/renal
Rosiglitazone	4-8	99%	>99%	4	CYP2C8 + (CYP2C9)	NO	P-gp	Renal
Dipeptidyl peptidase-4 inhibitors								
Linagliptin	5	30%	>80%	Terminal >100	Minor (CYP3A4)	NO	P-gp	Bile (90% unchanged)
Saxagliptin	5	50%	Very low	2.5	CYP3A4	YES	P-gp	Renal (24% unchanged)
Sitagliptin	100	87%	38%	12	Minor (CYP3A4 + CYP2C8)	NO	hOAT3, OATP4C1, P-gp	Renal (79% unchanged)
Vildagliptin	50-100	85%	9%	3	Hydrolysis, no CYPs involved	YES	P-gp	Renal (23% unchanged)

1.2 Problem statement and significance of the study

Nowadays, T2DM disorder is significantly rising worldwide including Palestine. According to the Annual Palestinian MOH reports published in June 2020; 5,671 recent cases were registered in primary healthcare centers in Palestine in 2019 (health, 2020).

From a clinical perspective, such diseases need diverse types of medications and numerous modalities of treatment to ensure well-controlled patient status. Therefore, risks for potential DDIs incidences are often reported.

Right now, in Palestine there is an absence of published research focusing on evaluation of the potential DDIs among T2DM patients. To the best of our knowledge, this study is the first examining and discussing this issue. For the purpose of minimizing the occurrence and subsequent consequences of DDIs, pharmacists, clinicians, healthcare professionals and researchers need to be more knowledgeable and better experienced about these interactions. When healthcare providers succeed at avoiding the fall in DDIs; patients' quality of life improves and more effective patients' care can be achieved and decreased healthcare costs.

1.3 Objectives

1.3.1 General objectives

The main aim of the current study is to evaluate the potential DDIs among medications prescribed for T2DM patients at the primary healthcare setting in southern West Bank.

1.3.2 Specific objectives

1. To determine the prevalence of DDIs among T2DM patients.
2. To assess the modalities of DDIs among T2DM patients.
3. To find out the most common DDIs among their medications.
4. To examine factors associated with potential DDIs among those patients.
5. To discern the distribution of potential DDIs according to patient's gender, age, complications, polypharmacy and comorbidities.
6. To evaluate the relationship between HbA1c and potential DDIs.
7. To evaluate the relationship between HbA1c and complications.

Chapter Two
Literature review

2. Literature review

Several studies have been published addressing DDIs. The literature collected and listed in this section were accessed from online data bases where only English language papers available were reviewed. All studies accessed were international studies, and the most relevant topics are chosen focusing on DDIs among medications prescribed to patients at national, regional and international levels. The chosen themes include the following:

2.1 In the world

✓ In 2015, Samardzic and Bacic-Vrca published a study examining the incidence and type of potential DDIs of anti-diabetic drugs in patients with diabetes, subdivided into 6.3 % T1DM and 93.7% T2DM. A round the half of participants were female, with 66 as the mean age of study participants. They found that 80.9% of patients had at least one potential category C interaction, no D and X category interactions between their anti-diabetic drugs and other prescribed medications (Samardzic & Bacic-Vrca, 2015).

✓ A prospective study was conducted in Manipal Teaching Hospital in Nepal (2006), analyzed 182 patient's prescriptions; 685 different drug were enrolled (Durga & Pharm, 2007). The study reveal that age over 50 years had a higher risk for developing DDIs. Metformin was responsible for the

majority of DDIs, a combination of Metformin with Enalapril was the most common potential DDIs among participants.

✓ In a recent study (2017) conducted by Hammad, Mohamed Anwar et al. (Hammad et al., 2017), in Penang general hospital, aimed to reveal DDIs among uncontrolled glycemic patients. The participant's patients had multiple comorbidities with multiple prescribed medications. The study disclosed that 23% of uncontrolled glycemic patients had at least one potential DDIs. The potential of DDIs that noticed among patients depends on the type of comorbidity and medication.

✓ In Kenya, especially in Kisii teaching and referral hospital, a quantitative cross-sectional study was conducted, by Eric Ogamba Otachi 2016 (Otachi, 2016a). The study was done to investigate the prevalence of DDIs among patients receiving both hypoglycemic and antihypertensive drugs. 168 medical records data have been reviewed, 96% prescriptions had at least one potential DDIs, 5% of the potential DDIs were classified as major interactions, while 50% were moderate. In conclusion, the prevalence of potential DDIs was high, all prescriptions should be checked and analyzed by prescribers and dispensers before dispensed.

✓ An original article conducted in 2005 by Ibrahim A. Ibrahim et al. (IbrahimKang, & Dansky, 2005) aiming to examine the possibility of DDIs in their prescribed medications and the prevalence of polypharmacy among a group of home healthcare elderly diabetic patients, it was a retrospective study consisted of 139 diabetic patients, nearly all the patients 92.8% could

potentially have moderate DDIs, 8.9 was the average number of medications taken by the patients per prescription, which reflect that the potential of experiencing polypharmacy among their prescriptions is too high that was 88%.

✓ Oct 2015, an article have been published by Veintramuthu Sankar et al. (Sankar et al., 2015), to identify the potential DDIs in the prescriptions prescribed for diabetic inpatients in multi-specialty hospital hospital in India, revealed 70% of the prescriptions with drug interaction, 90% of the prescription down to polypharmacy. Cardiac drugs, analgesic drugs, antibiotic drugs, anti-diabetic drugs respectively were the most common classes of drugs causing DDIs. In conclusion, screening of prescriptions by healthcare providers should be one of the most important goals in drug therapy.

✓ A review paper published by Marcus May and Christoph Schindler (2016) (May & Schindler, 2016), focused on patients with type 2 diabetes mellitus, for showing clinically and pharmacologically relevant interactions of anti-diabetic drugs. The vast majority of these patients were living with different comorbidities; hypertension, dyslipidemia, renal disease, and peripheral artery disease, which require multifactorial pharmacological treatment to control their medical conditions. Their concomitant use of drugs makes them more prone to drug interaction, such as the relevant and predominant interaction among SUs, TZD and glinides. Although

metformin has a very low interaction potential, caution is advised when drugs that impair renal function are used simultaneously.

✓ A Comprehensive Review conducted by Stage et al., (2015) (Stage et al., 2015), revealed that Metformin (reduction of hepatic glucose production (biguanides)), is the world's most commonly used form of OADs for T2DM patients, mainly because it protects against diabetes-related mortality and all-cause mortality. Notably, there is considerable inter individual variability in the response to metformin. The elimination rate of the drug is mainly determined by renal function, in which several specific (OCT1) and (OCT2) are involved. Thus, all drugs affecting renal function are likely to be more sensitive to many metformin DDIs.

✓ In 2009, Andreas Holstein & Winfried Beil (Holstein & Beil, 2009) addressed the metabolism of OADs, and their associated drug interactions. The study revealed a high incidence of drug interactions accompanying concurrent use of OADs, especially with which pharmacokinetic profile shows interferences through the CYP450 system. TZDs, SUs or meglitinides are exposed to numerous pharmacokinetic interactions, as these compounds undergo major hepatic metabolism through different CYP450 enzymes. Meanwhile, metformin and acarbose are not metabolized by CYP450 enzymes and, therefore, have safe pharmacokinetic profiles lacking potential DDIs.

✓ Another study conducted by André J. Scheen (2005)(Scheen, 2005), has explored potential DDIs with anti-hyperglycemic agents. There is a higher risk of hypoglycemic episodes associated with co-prescribed anti-hyperglycemic agents, such as the classical dual therapy of SUs and metformin, SUs plus TZDs and the biguanide compound metformin plus TZDs. Even if modest pharmacokinetic interferences have been reported with these combinations, they do not appear to have important clinical consequences. On the other hand, comorbid conditions (e.g. lipid-lowering agents, antihypertensive agents), and other agents known to induce or inhibit the CYP450 system, are more susceptible to elicit relevant DDIs in T2DM patients.

✓ A study from Switzerland, published in October of 2015 by Devineni D and Polidori D (Devineni & Polidori, 2015), found that the new class of oral agents selective SGLT2 inhibitors (canagliflozin)- which work by decreasing the renal threshold for glucose (RTG) and increase urinary glucose excretion (UGE) in the kidney- has moderately increased clinical DDIs if co-administered with rifampicin. These will reduce its plasma concentrations and thus need further glycemic control monitoring, while no significance DDIs with metformin, glyburide, simvastatin, warfarin, hydrochlorothiazide, oral contraceptives, probenecid and cyclosporine.

✓ Also in Switzerland, a study aimed at reviewing potential DDIs with selective inhibitors SGLT2 (dapagliflozin, canagliflozin and empagliflozin). It was done by Scheen AJin in 2014 (Scheen, 2014), which

found that plasma drug levels of each SGLT2 has no clinically relevant influences when administered concomitantly with other glucose-lowering agents or cardiovascular agents. Meanwhile, potential DDIs with T2DM on chronic treatment with SGLT2 are expected when receiving medications concomitantly interfering with the metabolic pathway of SGLT2 inhibitors such as rifampicin. Rifampicin is an inducer for the uridine diphosphate glucuronosyl transferase (UGT) enzyme, which is responsible of glucuronidation of Canagliflozin into two inactive metabolites.

✓ A summarized review conducted in 2010 (Scheen, 2010a), reported that DDIs for five DDP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin showed that no or only minor DDIs have been reported between DDP-4 and antidiabetic drugs, according to pharmacokinetic findings subjected on healthy young male cases. Saxagliptin -metabolized by CYP3A4/5 into an active metabolite and the only exception between DDP-4 inhibitors- requires specific caution when co administered with specific strong inhibitors (ketoconazole, diltiazem) or inducers (rifampicin) of CYP3A4/5 isoforms (Scheen, 2010a).

2.2 In Palestine

In Palestine there are no local studies addressing DDIs among DM patients. Yet, few studies were performed in Palestine related to the DDIs in general, one of which is a study conducted by Al Ramahi, et al. (2016) (Al-Ramahi et al., 2016) to evaluate potential DDIs in hemodialysis (HD) patients. As a commonly comorbid condition present in HD patients, the

study revealed that a total of 275 patients were interviewed, 245 (89.1 %) of them had at least one potential DDI. The possibility of interaction increases with comorbidities. Hypertension, DM, gout, myocardial infarction, hyperlipidemia, and congestive heart failure respectively, were the most commonly comorbid conditions present in the HD patients, with different combinations present in each patient. The most frequent potential DDIs in 114 (41.5%) was Calcium carbonate/Amlodipine.

Another study conducted in Palestine considered with DDIs was done by Waleed M. Sweileh et al. in Palestine, 2003 (SweilehSawalha, & Jaradat, 2005), to investigate DDIs among patients with cardiac disease receiving antihypertensive medications. A retrospective study, which was evaluated 876 medical files for patients receiving one or more antihypertensive medications. The study revealed that both age and increasing number of medications were significantly associated with the potential of DDIs, 40% was the prevalence of DDIs with medications typically used for to treat hypertensions.

Currently 2020, there was a research article conducted in three Palestinian hospitals among patients admitted to surgery departments for assessing DDIs with identifying their associated factors(RabbaAbu HusseinAbu Sbeih, & Nasser, 2020). 502 patients were included; 56% of the total number of patients had at least one potential DDIs, according to severity of drug interactions 52.7% was major. Age, number of medications and duration of hospital stay were possibly associated with having DDIs. In

surgery department, the patient are more prone to have common DDIs resulting by antibiotic s and analgesics.

In Palestine, a study considered with evaluating the potential DDIs in elderly patients (DiakAlsaberAlsaberFadel, & Halayqa, 2016), by Aya Abu Diak et al., was completed in 2016, in two healthcare centers in Nablus, by interviewing 393 patients in addition to reviewing their medical record. The study resulted in; the prevalence of DDIs among elderly patients was very common, increasing the number of medication used by the patients is significantly associated with increasing potential DDIs.

A retrospective study in 2020, mediated by Iyad Ali et al. (AliBazzarHussein, & Sahhar, 2020), the study aimed to evaluate the frequency and severity of potential DDIs among ICU patients in three hospital in Nablus, Palestine. Out of the total number of participating patients;72% of them had at least one DDIs, 66.6% were moderate interactions and their past medical history revealed that they had comorbidities; 29% had hypertension, 25% had DM, and ischemic heart disease (IHD) 10%.

Chapter Three
Methodology

3. Methodology

3.1 Study design

The study was an observational prospective survey employing cross-sectional design among T2DM patients, to evaluate potential DDIs among prescribed medications in primary healthcare centers.

3.2 Study setting

The study included 400 patients with T2DM. It was conducted at a number of governmental primary healthcare centers include outpatient clinics for DM disease in the Southern part of West Bank; Hebron and Bethlehem between July and September 2018.

3.3 Population of the study and selection criteria

All T2DM patients whom visited the primary healthcare centers in the Southern part of the West Bank; Hebron and Bethlehem district. Over 3-month period were patients come to these centers monthly to receive their medications for their chronic disease free (if they have a governmental health insurance).

The inclusion criteria used in this study were all T2DM patients, who had at least three months consecutive follow up. However, patients with mentally unstable; due to the difficulty of conducting the interview with

them, critically ill, pregnant women and all patients who don't visit primary healthcare centers for their cases were excluded.

3.4 Sample size

According to the MOH records of 2017 in Palestine (health, 2018) , the total number of T2DM patients at the Southern districts of West Bank was 13470, which accounts towards a third of the total number of T2DM patients in the West Bank (i.e., 41555). Based on these figures, the required sample size was estimated using the Raosoft sample size calculator (http://www.raosoft.com/samplesize.html) with a 5% predetermined margin of error, and confidence level of 95%. The target of the sample was set at approximately 400 diabetic patients. Table 2 lists some statistical data about MOH clinics distributed in the West Bank.

Table 2: **Distribution of MOH Clinics, Chronic Diseases and T2DM in West Bank.**

City	*No. of population*	*MOH Clinics*	*Chronic Disease*	*T2DM*
Jenin	308,618	53	12243	6452
Tubas	60,186	11	2538	1323
Tulkarm	183,205	31	8676	4658
Nablus	387,240	44	9416	4765
Qalqiliya	108,234	22	4743	2019
Salfit	73,756	18	4728	2225
Ramallah	322,193	56	5996	3771
Jeriho	50,002	10	1357	830
Jerusalem	154,320	27	2754	2042
Beit lahem	215,047	21	4854	2545
Hebron	707,017	120	19861	10925
Total / West Bank	2,569,818	413	77166	41555

3.5 Data collection form and management

The patients in this study were seen at primary healthcare centers, who regularly visited these centers during the study period and were using at least one diabetic medication chronically. Previous the beginning of interview the patient have been asked to participate in the study.

Data collection tool was questionnaire, which was completed by interviewing a convenience sample of Patients. The questionnaire subdivided into three parts. Part (1): patient's information about socio-demographic characteristics; gender, age, marital status, education, employment status. Part (2): medical history of patients; their checkups, complications and tests. Part (3): management and treatment used, in which patients asked about their co-morbidities, history of medications use, indications and frequency Appendix B**.**

Only prescribed medications from MOH clinics and their dosage regimens were documented from the most recent prescription. We decided to exclude OTC medication, that wasn't mentioned in their prescriptions, as they considered to have widely safer used, the difficulty to document and the universality of access to them by all patients. Furthermore, different types of insulin were considered as one drug and documented as one insulin category. For gathering additional data, especially for their comorbidities and specific checkups, their medical records were reviewed, besides interviewing them.

Potential DDIs were identified by using Lexi-Comp® electronic database ("lexi-Comp ", 2019), which was a software online interaction checker, by which all prescribed medications were included submitted into the application, for the purpose of screening for potential DDIs with its mechanism of action and categorizes DDIs according to severity . Each interaction was assigned a risk rating of A, B, C, D, or X, according to their clinical significance: Risk rating (A) means no known interaction; (B) no action is needed; (C) requires monitoring therapy; (D) requires considering therapy modification, and (X) contraindication means we should avoid combination Table 3.

Table 3: definitions of risk rating of DDIs

Risk rating	***Action***	***Description***
A	**No known interaction**	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.
B	**No action needed**	Data demonstrate that the specified agents may interact with each other, but there is little to no evidences of clinical concern resulting from their concomitant use.
C	**Monitor therapy**	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	**Consider therapy modification**	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient- specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.
X	**Avoid combination**	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

3.6 Ethical consideration

The study protocol was authorized by local institutional review boards (IRB) of An-Najah National University (04, April 2018**)** Appendix C and the Palestinian MOH (12, June 2018) Appendix D before initiation of this study. All subjects had been informed of their rights to refuse or discontinue participation in the study according to the ethical standards. Informed verbal consent from the participants was obtained before beginning the interviews.

3.7 Statistical analysis

Statistical analysis was performed by using the Statistical Package for Social Sciences (SPSS software version 21). Mean ± standard deviation , or median were also given for continuous data. Frequencies and percentages were included for all variable as appropriate. Mann-Whitney-U test was used to determine if there are statistically significant differences between two groups of an independent variable on a continuous dependent variable, meanwhile Kruskal-Wallis test was used to determine the differences between two or more independent variable on continuous dependent variable. Univariate analysis is the simplest form of analyzing data, looking at single variable, is typically the first procedure one does when examining first time data, univariate analysis was used to find factors associated with DDIs; included data explore, descriptive analysis and explore frequencies, mean, count and standard deviation. A P-values < 0.05 was considered to be statistically significant for all analyses.

Chapter four
Results

4. Results

4.1 Socio-demographic characteristics of participating patients

During the study period, a total of 400 patients were interviewed. All of them successfully responded to the questionnaire (response rate was 100%). Among the patients, the majority were aged over 60 years (183, 45.8%), the lowest age of the participant was 38 years and the oldest was 89, females (248, 62.0%), living in villages (247, 61.8%). Regarding their educational level, the highest percentage of patients were had primary school (185, 46.3%), while (47, 11.8%) of them had a college or university degree Table 4

Table 4: Socio-demographic characteristics of the 400 patients

Characteristics	Frequency	Percentage
Age		
31-40	**2**	**0.5%**
41-50	**54**	**13.5%**
51-60	**161**	**40.3%**
>60	**183**	**45.8%**
Gender		
Male	**152**	**38.0 %**
Female	**248**	**62.0 %**
Living place		
City	**153**	**38.3 %**
Village	**247**	**61.8 %**
Educational level		
Primary	**185**	**46.3 %**
High school	**65**	**16.3 %**
University	**47**	**11.8 %**
None	**103**	**25.8 %**

4.2 Drug prescribed

During the study period, a total of 114 different medications were used by the patients. The patients were taking a minimum of one and a maximum of 20 medications. The most commonly prescribed medications were metformin, being used by 85.5% patients. Followed by atorvastatin, ASA, glimepiride and enalapril, which were used by 74.5%, 74.0%, 44.3%, 32.3% of patients respectively Table 5.

However, detailed results were listed in the Appendix E which reports all prescribed medications.

Table 5: Top 20 prescribed medications used by patients included in the study

No.	Medication	Frequency	Percentage
1.	**Metformin**	342	85.5 %
2.	**Atorvastatin**	298	74.5 %
3.	**Acetyl salicylic acid**	296	74.0 %
4.	**Glimepiride**	177	44.3 %
5.	**Enalapril**	129	32.3 %
6.	**Amlodipine**	122	30.5 %
7.	**Ranitidine**	112	28.0 %
8.	**Bisoprolol**	107	26.8 %
9.	**Furosemide**	106	26.5 %
10.	**Carbamazepine**	83	20.8 %
11.	**Alfacalcidol**	80	20.0 %
12.	**Calcium**	53	13.3 %
13.	**Losartan**	47	11.8 %
14.	**Allopurinol**	44	11.0 %
15.	**Clopidogrel**	43	10.8 %
16.	**Hydrochlorothiazide**	35	8.8 %
17.	**Omeprazole**	35	8.8 %
18.	**Atenolol**	32	8.0 %
19.	**Spironolactone**	23	5.8 %
20.	**Valsartan**	21	5.3 %

4.3 Co-morbid conditions

Cardiovascular diseases, dyslipidemia, gout, infectious disease which caused by pathogenic microrganisms, and thyroid, were the most commonly co-morbid conditions diagnosed in the DM participating patients, with a different combination between these conditions in each patient. 90.5% was the prevalence of DDIs in patients with comorbidities, the contribution as follow; 77.3% had cardiovascular diseases, dyslipidemia 64.5%, gout 12.0%, infectious diseases 9.5%, thyroid disease 5.5%, and asthma 3.5% Table 6.

Table 6: Concomitant medical conditions and comorbidities among DM patients

No.	Disease	Frequency	Percentage (%)
1.	Cardiovascular disease	309	77.3 %
2.	Dyslipidemia	258	64.5 %
3.	Gout	48	12.0 %
4.	Infectious disease	38	9.5 %
5.	Thyroid	22	5.5 %
6.	Asthma	14	3.5 %
7.	Benign Prostatic Hypertrophy	12	3.0 %
8.	GI Upset (chronic or transient)	10	2.5 %
9.	Allergy (chronic or transient)	10	2.5 %
10.	Neurologic disorders [2]	7	1.8 %
11.	Cancer	3	0.8 %
12.	Surgery	2	0.5 %
13.	Renal disease	1	0.3 %
[2] Al diseases of the brain, spine, and the nerves that connect them, affect millions of people each year			

4.4 Most common combination

The most common interaction was 61.5 % Acetyl salicylic acid with Metformin followed by Glimepiride with Metformin in 40.5 % cases. Table 7 shows the top 20 potential interactions while Appendix G shows all potential DDIs and Table 8 shows description of these interaction.

Table 7: Top 20 potential DDIs.

No.	Drug-drug interactions	Percent	Risk rating	Severity
1.	ASA/Metformin	61.5%	C	Moderate
2.	Glimepiride/Metformin	40.5%	C	Moderate
3.	Glimepiride/ASA	33.0%	C	Moderate
4.	Metformin/Enalapril	28.3%	C	Moderate
5.	Enalapril/ASA	24.3%	C	Moderate
6.	Insulin/Metformin	20.5%	C	Moderate
7.	ASA/Furosemide	20.5%	C	Moderate
8.	Metformin/Furosemide	19.3%	C	Moderate
9.	Atorvastatin/Carbamazepine	15.8%	D	Slightly severe
10.	Glimepiride/Enalapril	14.5%	B	Minor
11.	Insulin/Enalapril	13.3%	B	Minor
12.	Insulin/Furosemide	12.3%	C	Moderate
13.	Alfacalcidol/Calcium	11.5%	C	Moderate
14.	Glimepiride/Ranitidine	10.3%	C	Moderate
15.	ASA/Calcium	10.3%	B	Minor
16.	Clopidogrel/Atorvastatin	9.8%	B	Minor
17.	ASA/Clopidogrel	9.3%	C	Moderate
18.	Insulin/Bisoprolol	9.0%	C	Moderate
19.	Enalapril/Furosemide	8.8%	C	Moderate
20.	Glimepiride/Furosemide	8.8%	C	Moderate

Table 8: Description of top twenty DDIs

No.	DDIs combinations	Cause and effect
1.	ASA/Metformin	Salicylates may enhance the hypoglycemic effect of blood glucose lowering agents.
2.	Glimepiride/Metformin	Antidiabetic agents may enhance the hypoglycemic effect of hypoglycemia-associated agents.
3.	Glimepiride/ASA	Salicylates may enhance the hypoglycemic effect of blood glucose lowering agents.
4.	Metformin/Enalapril	ACE inhibitors may enhance the adverse / toxic effect of metformin. This includes both a risk for hypoglycemia and for lactic acidosis.
5.	Enalapril/ASA	Salicylates may enhance the nephrotoxic effect of ACE inhibitors. Salicylates may diminish the therapeutic effect of ACE inhibitors.
6.	Insulin/Metformin	Antidiabetic agents may enhance the hypoglycemic effect of hypoglycemia associated agents.
7.	ASA/Furosemide	Salicylates may diminish the diuretic effect of Loop Diuretics. Loop Diuretics may increase the serum concentration of Salicylates.
8.	Metformin/Furosemide	Hyperglycemia associated agents may diminish the therapeutic effect of antidiabetic agents.
9.	Atorvastatin/Carbamazepine	Carbamazepine (CYP3A4 Inducers / strong) may increase the metabolism of Atorvastatin (CYP3A4 Substrates).
10.	Glimepiride/Enalapril	ACE inhibitors may enhance the hypoglycemic effect of blood glucose lowering agents
11.	Insulin/Enalapril	ACE inhibitors may enhance the hypoglycemic effect of blood glucose lowering agents
12.	Insulin/Furosemide	Hyperglycemia-Associated agents may diminish the therapeutic effect of antidiabetic agents.
13.	Alfacalcidol/Calcium	Calcium salts may enhance the adverse / toxic effect of Vitamin D analogs.
14.	Glimepiride/Ranitidine	Ranitidine may increase the serum concentration of Sulfonylureas.
15.	ASA/Calcium	Antacids may decrease the serum concentration of salicylates.
16.	Clopidogrel/Atorvastatin	Atorvastatin may diminish the antiplatelet effect of clopidogrel.
17.	ASA/Clopidogrel	Agents with antiplatelet properties may enhance the adverse / toxic effect of salicylates. Increased risk of bleeding may result.
18.	Insulin/Bisoprolol	Beta blockers may enhance the hypoglycemic effect of insulins.
19.	Enalapril/Furosemide	Loop diuretics may enhance the hypotensive effect of ACE inhibitors. Loop diuretics may enhance the nephrotoxic effect of ACE inhibitors.
20.	Glimepiride/Furosemide	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents.

4.5 Evaluation of potential DDIs

In the current study, a total of 2627 potential interactions were identified. Out of the included 400 patients, 384 (96 %) patients had at least one potential DDIs, meanwhile 16 patients hadn't Figure 1. Table 4.6 shows the prevalence of DDIs among the patients.

Figure 2 shows the frequencies of the number of DDIs per prescription.

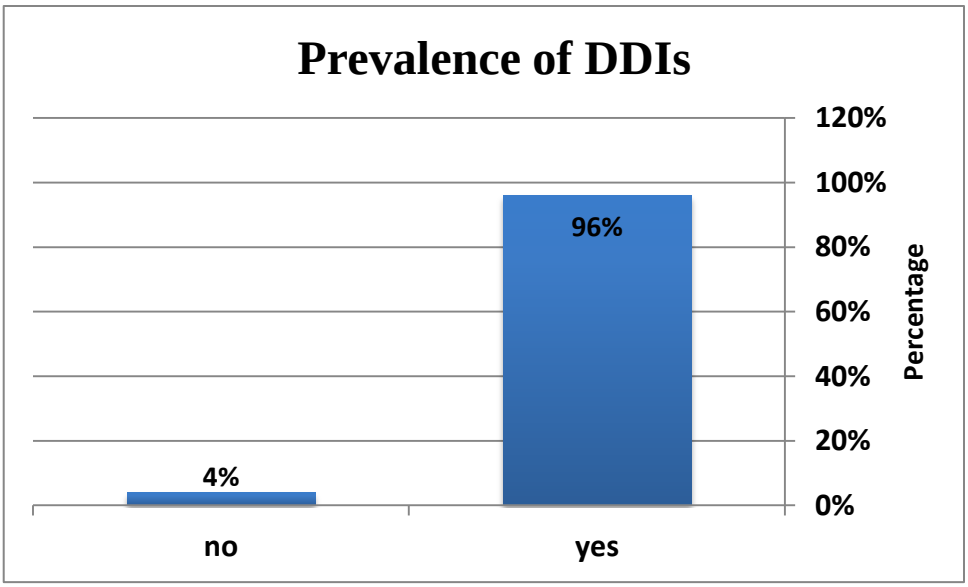

Figure 1: The prevalence of DDIs.

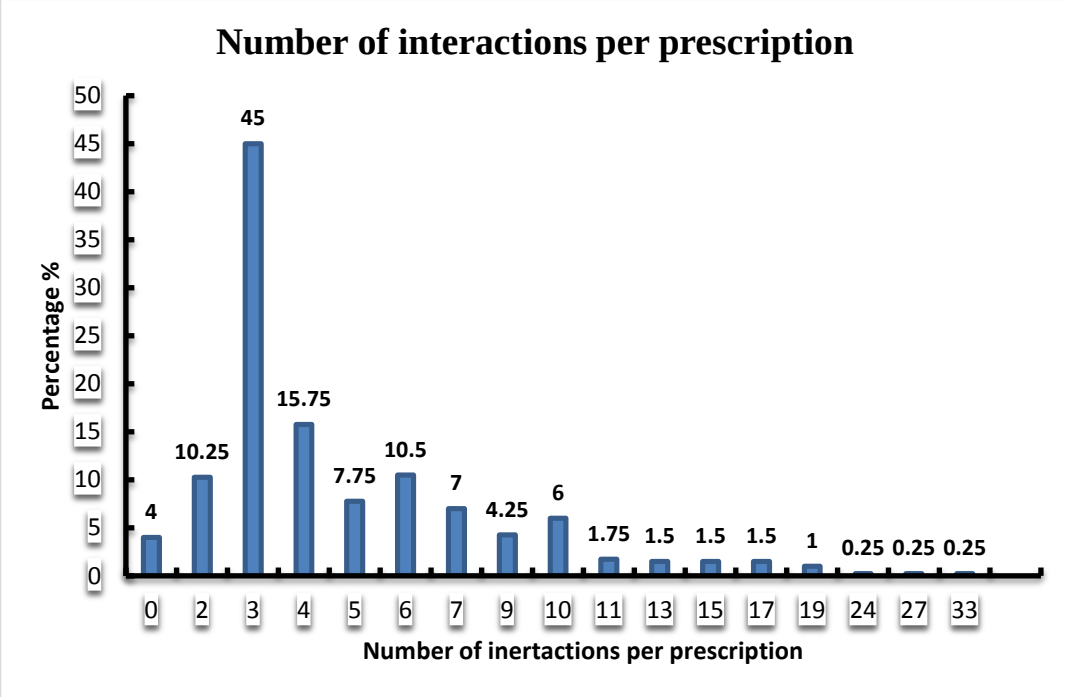

Figure 2: The frequency of the number of potential DDIs for patients.

4.6 The prevalence of DDIs among associated factors.

In Table 9 below, it was explained how the percentage of DDIs (96%) for the patients were distributed among associated factors. It was revealed that around of 60% of DDIs appeared in female, a little less of the half of DDIs with patients over 60 year, third of DDIs were associated with patients with nephropathy as a complications of T2DM, the majority of DDIs were appeared in patients had polypharmacy and comorbidities in their cases (73.0%) (90.5%) respectively.

Table 9: The prevalence of DDIs among associated factors.

Characteristic	Category	Frequency of DDIs	Prevalence of DDIs
Gender	Men	145	36.2%
	Female	239	59.8%
Age	31-40	2	0.5%
	41-50	46	11.5%
	51-60	156	39.0%
	>60	180	45.0%
Complications	N.A	160	40.0%
	Nephropathy	122	30.5%
	Neuropathy	78	19.5%
	Retinopathy	22	5.5%
	Diabetic foot	2	0.5%
Polypharmacy	<5	61	15.0%
	5-10	291	73.0%
	>10	32	8.0%
Comorbidities	Yes	362	90.5%
	No	22	5.5%

4.7 Modalities of potential DDIs

Among the total number of identified potential interactions (2627), according to risk rating classification, (35, 1.33 %) were A, (308, 11.72 %) were B, (2014, 76.67 %) were C, (263, 10.01 %) were D and (7, 0.27 %) were X Figure 3 Major risk potential drug interactions (Category D and category X) are demonstrated in Table 10, Table 11.

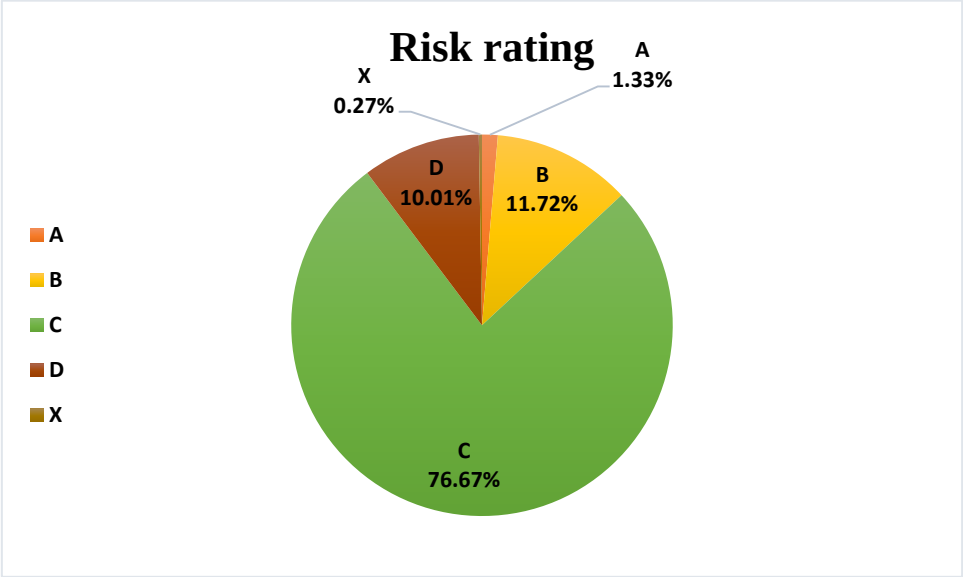

Figure 3: The risk rating of potential DDIs.

Table 10: Description of top five drug pairs with major risk rating (D category) DDIs.

NO.	Drug-drug interactions	Frequency	Percentage	Risk rating
1.	Atorvastatin/Carbamazepine	63	15.8%	D
2.	Amlodipine/Carbamazepine	23	5.8%	D
3.	Bisoprolol/Carbamazepine	20	5.0%	D
4.	Losartan/Carbamazepine	12	3.0%	D
5.	ASA/Indomethacin	6	1.5%	D

Table 11: Description of top five drug pairs with major risk rating (X category) DDIs.

NO.	Drug-drug interactions	Frequency	Percentage	Risk rating
1.	Sacubitril/Enalapril	1	0.3%	X
2.	Celecoxib/Indomethacin	1	0.3%	X
3.	Acetazolamide/Topiramate	1	0.3%	X
4.	Acetazolamide/Dorzolamide	1	0.3%	X
5.	Etoricoxib/Indomethacin	1	0.3%	X

4.8 Factors associated with potential DDIs

Univariate analysis showed a significant correlation between age and number of potential interactions (p value < 0.001)). The number of potential DDIs that the patients had were also related to their educational level, as well as comorbidities, number of medications and complications (p value < 0.001 for each one). However, there was no significant relationship with gender and (p value = 0.404), marital status and the number of potential DDIs (p value = 0.088), or smoking and the number of potential DDIs (p value = 0.279) as shown in Table 12.

Table 12: Factors associated with potential DDIs.

Characteristics	Frequency N=400	Number of DDIs Median (Q1 – Q3)	P-value
Gender			
Male	152 (38 %)	5 (3 - 8.75)	0.404
Female	248 (62 %)	6 (3 - 9)	
Age category			
31-40	2 (0.5 %)	2.5 (2 - 3)	0.000**
41-50	54 (13.5 %)	3 (1 -6)	
51-60	161 (40.25 %)	5 (3 - 8)	
>60	183 (45.75 %)	6 (3 - 10)	
Marital status			
Single	4 (1 %)	6 (4 -11.5)	0.088
Married	357 (89.25 %)	5 (3 -9)	
widowed	37 (9.25 %)	7 (3 -14)	
Divorced	2 (0.5 %)	2 (1 -3)	
Educational level			
Primary	185 (46.25 %)	6 (3 - 9)	0.000**
High school	65 (16.25 %)	4 (1 - 8)	
Bachelor	47 (11.75 %)	4 (1 - 6)	
None	103 (25.75 %)	6 (3 - 10)	
Smoking			
Smoker	347 (86.75 %)	5 (2.5 - 8)	0.279
Non smoker	53 (13.25 %)	5 (3 -9)	
Comorbidities			
Yes	373 (93.3 %)	6 (3 – 9)	0.000**
No	27 (6.8 %)	1 (1 – 3)	
Number of medications			
<5	76 (19 %)	1 (1 - 3)	0.000**
5 – 10	292 (73 %)	6 (4 - 9)	
>10	32 (8 %)	16.5 (13.25 - 20)	
Complications			
Yes	227 (65.8%)	7 (3 -10)	0.000**
No	173 (43.2%)	4 (1.5 – 6)	

4.9 Relationship between age category and the number of drug prescribed per prescription and complication.

From the current prospective observational study, it was documented a direct correlation between the age and this two variables; the number of drugs prescribed and complications Table 13.

Table 13: correlation between age category and the number of drug prescribed per prescription and complications.

		Number of drugs prescribed			Complications			
		<5	**5-10**	**>10**	**Nephron**	**Neuro.**	**Retino.**	**D.foot**
Age	**31-40**	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	41-50	4.5%	8.8%	0.2%	4.7%	1.2%	0.5%	0.0%
	51-60	9.0%	29.2%	2.0%	13.8%	5.8%	1.2%	0.0%
	> 60	5.0%	35.0%	5.8%	12.8%	12.5%	3.8%	0.5%

4.10 Controlled vs uncontrolled HbA1c

It was observed that among 400 patients with T2DM who were scanned for HbA1c% test, 396 (99.0%) of them had HbA1c% test in the past 3 months while the 4 (1.0%) patients had not. From 396 patients with HbA1c % test, Only 107 (26.8%) cases had controlled glycemia while 289 (72.3%) cases with un controlled glycemia.

Table 14 below shown there is an association relationship between the presence of HbA1c and complication (P-value 0.000). Meanwhile, there are no differences between the HbA1c test and the presence of DDIs (P-value 0.03) as shown in Table 15.

Table 14: Association relationship between HbA1c and complication.

HbA1c	Count	percentage	Complications			Sig.
			Complications	Count	Percentage	
Controlled A1C < 7%	107	26.8%	Yes	39	36.4%	**0.000***
			No	68	63.6%	
Uncontrolled A1C >7%	289	72.3%	Yes	186	64.4%	
			No	103	35.6%	

Table 15: Association relationship between HbA1c and DDIs.

HbA1c	Count	percentage	DDIs			Sig.
			DDIs	Count	Percentage	
Controlled A1C < 7%	107	26.8%	Yes	100	93.5%	0.03
			No	7	6.5%	
Uncontrolled A1C >7%	289	72.3%	Yes	280	96.9%	
			No	9	3.1%	

Chapter Five
Discussion

5. Discussion

The highest occurrence of DDIs in our study was detected among patients aged over 60 years with a percentage of 45.0%. Similarly, a study done by Dinesh K U et al., in 2007 (Durga & Pharm, 2007) revealed that DDIs had high prevalence in patients older than 50 years. This finding also was in agreement with a large Swedish population-based study applied by Astrand, Bengt et al., in 2006 (ÅstrandÅstrandAntonov, & Petersson, 2006). Positive correlations were seen between age groups and the incidence of DDIs, due to changes in pharmacokinetic and pharmacodynamics interactions. Besides, elderly patients are more prone to have more than disease, so they need to take more medications to control their conditions.

In the current study we perceived that the most frequently prescribed medications were metformin followed by atorvastatin, acetyl salicylic acid, glimepiride and enalapril. Similar to the study in 2007 by Dinesh et al. (Durga & Pharm, 2007) , comprising of 182 patients and 685 different medications, metformin was the most commonly prescribed medication, followed by enalapril and atenolol. This was almost consistent with another study published in 2015 by the Stage research team (Stage et al., 2015), metformin was also the most commonly prescribed medication, this compatibility was due to that metformin considered the mainstay OADs

drug for T2DM patients, and the first choice treatment, decreasing the mortality rate associated with diabetic patients.

Our study declared a significant association between the presence of comorbidities and DDIs in T2DM patients, the study shown that 90% of DDIs was in patients had comorbidities. The most common disease was cardiovascular disease, dyslipidemia, gout, infectious diseases and thyroid disease respectively. Sanker et al. (Sankar et al., 2015), found that the most common disease associated with T2DM patients were infections, followed by hypertension and dyslipidemia. This difference in the prevalence of comorbidities with DMT2 may appear as a result of the variation in study participants; physiological and pharmacological aspects may be the main cause.

In the present study, a combination of acetyl salicylic acid with metformin had the highest prevalence of DDIs among T2DM. Acetyl salicylic acid may enhance the hypoglycemic effect of blood glucose lowering agents ("lexi-Comp ", 2019). Meanwhile, the combination of acetyl salicylic acid and insulin was the drug combination with the highest prevalence to cause moderate DDIs as presented by Sanker et al. (Sankar et al., 2015). Metformin and Enalapril was the most common combination was appeared in another study conducted in Palestine Nepal by Dinesh and his co-workers (Durga & Pharm, 2007). Generally, these drugs are recommended as the first line choice for the management of DM and cardiovascular disease.

In this study, 400 patients received a total number of 114 different prescribed medications. About 96% of the patients had at least one potential DDI. Similar findings were stated by Otachi in Kenya who announced that 96% of prescriptions had at least one potential DDIs (Otachi, 2016b) and by Rodrigues, et al., in Saudi Arabia where about 90% of prescriptions present at least one DDIs (Rodrigues et al., 2015) However, a lower percentage (approximately two thirds) of included patients had at least one potential DDIs as reported by Sanker et al. (Sankar et al., 2015), the differences in the prevalence of DDIs perhaps due to healthcare provider's poor knowledge on basic information associated with DDIs, and perhaps due to differences in patient's compliance to their prescriptions in various countries.

Among all five classes of risk rating were observed in this study, moderate and minor interaction were the most commonly present, which require only appropriate rational drug therapy and contentious monitoring of potential DDIs as clinical management action. To add, the prevalence of moderate DDIs (76.67%) in this study was in fulfillment with the study published by Rodrigues et al., where 74% was reported as moderate DDIs (Rodrigues et al., 2015). In 2007, a study by Dinesh and his colleagues (Dinesh et al., 2007), their result was near to our result with a percentage of (92.1%) of moderate potential DDIs.

We found that a minimal number of potential major DDIs (0.27%) are clinically significant. Comprising of only 7 patients out of 400 participants of T2DM patients. Even when one major DDI is dangerous and life threatening to the patient, therapeutic effects of drug may be augmented or diminished if given together. This data was lower when compared with a previous study, Otachi in 2016 (Otachi, 2016b) found that the prevalence of major DDIs was 4%. In contrast, in study conducted in 2015 by Samardzic et al. (Samardzic & Bacic-Vrca, 2015) we found it free from DDIs of D and X category, that absence could be due to exclusion certain drugs that could cause D and X category DDIs with co-prescribed medications, and prescribers' awareness of their potential to cause DDIs with anti-diabetic drugs.

Evidently, the larger number of medications per prescription was significantly associated with high incidence of potential DDIs. We found that 73% of DDIs had a number of (5-10) medications, with 6 as the average number of interactions per prescription. This was comparable to other previous studies, such as a study carried out in Nairobi by Otachi in 2016 who found an average 5 potential DDIs per prescription (Otachi, 2016b). Polypharmacy with a high average of 6 drugs was expected because DMT2 is one of the most commonly present co morbid diseases with other conditions, their prescriptions are more predisposed to have DDIs.

Johnell and Klarin, reported a strong relationship between the number of prescribed drugs and the possibility of DDI incidences (Johnell & Klarin, 2007). T2DM patients are more prone to have multiple drugs prescribed in their regimens due to their comorbidities. In this study, we found that 114 different medications were used by the patients supporting the finding of Dookeeram and co-authors, which state that polypharmacy and certain common chronic diseases (hypertension, DM, psychiatric diseases) were significantly associated with potential DDIs (Dookeeram et al., 2017).

From 400 patients, 396 patients had regular HbA1c test, and the result included that only 107 (26.8%) cases had controlled glycemia while 289 (72.3%) cases with uncontrolled glycemia. In our study we detected that there is a correlation relationship between the reading of HbA1c and the appearance of complication, controlled glycemia mean less complications, the higher HbA1c the higher complications. According to the percentage related to controlled vs uncontrolled HbA1c, a study completed in 2017 by Hammad MA et al. (Hammad et al., 2017), revealed that 52.9% had controlled glycemia while 47.1% with uncontrolled glycemia. This differences in result perhaps due to not serious adhering of the patient to the required doses and regimens, along with the lack of strict commitment to the IDF guidelines by prescribers in managing T2DM patients.

Our data clearly indicate that there isn't a correlation relationship between HbA1c and DDIs, it is clear from the results that it is not a condition; the higher HbA1c means the greater interactions, the prevalence are the same

at the minimum and the highest level of HbA1c. this matches a study completed in 2015 by Samardzic, I. and Bacic-Vrca, V. (Samardzic & Bacic-Vrca, 2015). Patients with uncontrolled glycemia >7% mean more complications more comorbidities that require a higher number of medications beside to their anti-diabetic drugs, Meanwhile patients with controlled glycemia ≤7 had more anti-diabetics drug but less other drugs, anti-diabetics drug need more caution due to complex mechanism of action, and this could explain why there is no difference in DDIs with respect to HbA1c.

Chapter Six

Conclusions and recommendations

6.1 Conclusions

There was high prevalence of potential DDIs among T2DM patients at primary healthcare centers, which found to be associated with the large number of drugs taken by DM patients, especially dispensed to treat their concomitant complications and comorbid conditions. Metformin and ASA were the most common combinations. The majority of interactions were class C; moderate interaction. Age, comorbidities, complications, number of medications and education level were factors associated with the appearance of DDIs among T2DM patients.

This high prevalence reflects a knowledge gap among healthcare providers regarding DDIs. Providing DDI-related information to prescribers by updating data, ongoing researches, further educational programs and improving counseling to avoid improper use of medications by patients can play an important role in minimizing DDIs in diabetic patients.

6.2 Recommendations

✓ Clinical pharmacists should also play their vital role in improving patients' counseling to avoid improper DDIs due to self-medication.

✓ Physicians and pharmacists should take care while prescribing any OTC, natural products and any other concomitant medication and should be more aware of these potential interactions.

✓ In many cases, potentially interacting drugs can be given concurrently leading to the possibility of interaction. This interaction should be monitored and, if necessary, an intervention ought to be applied promptly to change doses or even therapy. In some situations, however, concurrent use of potentially interacting drugs should be avoided completely.

✓ Suspected adverse drug interactions should be reported to the appropriate regulatory authority as for other ADRs.

✓ The recognition of clinically significant interactions requires knowledge of the pharmacological mechanisms of drug interactions, which is highly recommended to include a clinical pharmacist among health care providers wherever they deliver their services.

✓ It is highly recommended to establish close teamwork between physicians and pharmacists immediately after the medication is prescribed.

✓ An updated database system or software to check drug interactions is recommended in all health care centers to screen the total prescriptions for every individual patient.

✓ It is imperative to take strict and necessary treatment measures in a manner that does not conflict with the medical protocol and drug interactions in order to delay the onset or further development of complications and comorbidities, by reducing HbA1c to achieve better glucose control.

6.3 Limitations and strength

Being a prospective study, getting all required data from interviewing patients was a challenge due to patient's integrity of reporting his/her information; some misinformation about patients' prescribed and may decrease the research accuracy.

We didn't monitor the patients for occurrence of DDIs clinically. Moreover, the generalization of the results is limited as the sample of patients was taken from the Southern part of the West Bank alone which may not be representative of all Palestinian DM patients.

However, this study is the first of its type in Palestine, and in the Arab world. It is also one of the few in the world. These results can give baseline data that can be useful in finding the prevalence of potential DDIs in patients with DM and identify factors associated with these interactions if present, as well as, in designing and implementing suitable interventions, educational programs and performing other related studies.

6.4 Future work

Further research paralleled with the ongoing study of pharmacokinetics, pharmacodynamics and drug interactions in co morbid disease is significant for safe and effective therapy and for the prevention of adverse drug reactions.

Increasing the knowledge base will enable more effective therapeutic interventions and improve the quality of life for the growing population of DM patients.

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Appendix

Appendix A

Criteria for the diagnosis of Diabetes.

	AIC ≥ 6.5% (48 mmol/mpl). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. *
OR	FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8h.*
OR	2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.*
OR	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

***in the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.**
A1C: Glycated Hemoglobin **A1c , NGSP:** National Glycohemoglobin Standardization Program**. DCCT:** Diabetes Control and Complications Trial**. FPG:** Fast Plasma Glucose, **OGGT**: Oral Glucose Tolerance Test, **WHO:** World Health Organization.

Appendix B

Questionnaire

An-Najah National University

Faculty of Graduate Studies
Master of Clinical Pharmacy

Exploring the potential drug-drug interactions among medications prescribed in primary health-care centers for T2DM patients.

A cross-sectional study from Palestine.

Part 1: Patient's information

Gender? □Male □ Female
How old are you? …….
Marital status? □ single □married □ widowed □divorced
Are you live with: □ Family □ Alone
Where do you live? □ City □ Village □ Camp
Do you smoke cigarettes? □ Yes □ No
Education: □ Primary school
□ Graduated high school
□ Bachelor's degree
□ Post graduate degree
□ None

Part 2: Medical History of Patients

Please state when you were first diagnosed with Diabetes: ……
Do you regularly test your blood for sugar/day? If yes, please state frequency of testing.
□Yes □No Frequency……
Please confirm the results of your most recent HbA1c, if known: HbA1c …….
Have you ever had any of the following? (If yes please tick all that apply).
□Yes □No
□ Nephropathy
□ Neuropathy
□ Retinopathy
□ Diabetic foot

Part 3: Management and treatment

How do you control your diabetes now? (Please tick all that apply)
□ Insulin
□ Tablets
□ Diet
□ Physical activity
Do you take any medication for any other condition? (If yes, please tick all that apply).
□Yes □No
Concomitant medical conditions:
□Cardiovascular disease
□Dyslipidemia
□neurologic disorders
□Infectious disease
□Renal disease
□Others
No. of medications prescribed: □ <5 □ 5-10 □ >10
Please tell us what treatment you are currently taking and provide full detail:
□Insulin □ Other diabetic medication

No.	*Name of med cation or treatment*	*Dosage*
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

Appendix C

IRB Approval Letter

An-Najah
National University
Faculty of medicine
&Health Sciences
Department of Graduate
Studies

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
دائرة الدراسات العليا

IRB Approval Letter

Study Title:

Evaluation of potential drug-drug interactions among medications prescribed in primary health-care centers for type 2 diabetes mellitus patients.

A cross-sectional study from Palestine.

Submitted by:

Sabrine Ra'fat Athamneh, Dr. Naser Shraim

Date Reviewed:

2nd April 2018.

Date Approved:

4th April 2018.

Your Study titled: **"Evaluation of potential drug-drug interactions among medications prescribed in primary health-care centers for type 2 diabetes mellitus patients. A cross-sectional study from Palestine"**. with archived number (1) April 2018 was reviewed by An-Najah National University IRB committee and was approved on 4th April 2018.

Hasan Fitian, MD

IRB Committee Chairman

An-Najah National University

IRB

نابلس - ص.ب 7 أو 707 || هاتف 2342902/4/7/8/14 (09) (970) || فاكسميل 2342910 (09) (970)

Nablus - P.O Box :7 or 707 | Tel (970) (09) 2342902/4/7/8/14 | Faximile (970) (09) 2342910 | E-mail : hgs@najah.edu

Appendix D

MOH Approval letter

State of Palestine
Ministry of Health - Nablus
General Directorate of Education in Health

دولة فلسطين
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Ref.:
Date:

الرقم: عدد/٥٠١٨/
التاريخ: ٢٠١٨/٦/١٤

الأخ مدير عام الادارة العامة للرعاية الصحية الاولية المحترم،،،

تحية واحترام،،

الموضوع: تسهيل مهمة طالبة- جامعة النجاح

يرجى تسهيل مهمة الطالبة: صبرين رأفت عثامنه- ماجستير صيدلة سريرية/ جامعة النجاح، في عمل بحث بعنوان: **تقييم التفاعلات الدوائية المحتملة بين الادوية الموصوفة لمرضى السكري من النوع الثاني في مراكز الرعاية الصحية الأولية**"، من خلال السماح للطالبة بجمع معلومات من خلال مقابلة المرضى لتعبئة استبانه ومراجعة ملفاتهم لجمع معلومات تتعلق بالبحث، وذلك في:

- مراكز الرعاية الصحية الاولية في منطقة جنوب الضفة (الخليل وبيت لحم)

علما ان البحث تحت اشراف د. نصر شريم. كما انه سيتم الالتزام بمعايير البحث العلمي والحفاظ على سرية المعلومات.

مع الاحترام،،

دولة فلسطين وزارة الصحة
الإدارة العامة للتعليم الصحي

مدير عام التعليم الصحي

نسخة: نائب الرئيس للشؤون الأكاديمية المحترم/ جامعة النجاح

Appendix E

List of all prescribed medications in participant DM patients

No.	*Medication*	*Frequency*	*Percentage (%)*
1.	Metformin	342	85.5 %
2.	Atorvastatin	298	74.5 %
3.	Acetylsalicalic acid	296	74.0 %
4.	Glimepiride	177	44.3 %
5.	Enalapril	129	32.3 %
6.	Amlodipine	122	30.5 %
7.	Ranitidine	112	28.0 %
8.	Bisoprolol	107	26.8 %
9.	Furosemide	106	26.5 %
10.	Carbamazepine	83	20.8 %
11.	Alfcalcidol	80	20.0 %
12.	Calcium carbonate	53	13.3 %
13.	Losartan	47	11.8 %
14.	Allopurinol	44	11.0 %
15.	Clopidogrel	43	10.8 %
16.	Hydrochlorothiazide	35	08.8 %
17.	Omeprazole	35	08.8 %
18.	Atenolol	32	08.0 %
19.	Spironolactone	23	05.8 %
20.	Valsartan	21	5.3 %
21.	Levothyroxine	19	4.8 %
22.	Sitaglptin	18	4.5 %
23.	Isosorbide mononitrate	15	3.8 %
24.	Vildagliptin.Met	13	3.3 %
25.	Acetaminophen	13	3.3 %
26.	Warfarin	12	3 %
27.	Indomethacin	11	2.8%
28.	Doxazocin	10	2.5 %
29.	Colchicin	9	2.3 %
30.	Cortisone	9	2.3 %
31.	Ibuprofen	9	2.3 %
32.	Digoxin	9	2.3%
33.	Amiloride	9	2.3%
34.	Iron	8	2 %
35.	Salbutamol	8	2 %
36.	Timolol	7	1.8%
37.	Ramipril	6	1.5 %
38.	B 12	6	1.5 %
39.	Budesonide	6	1.5 %
40.	Cefuroxime	6	1.5 %
41.	Glibeclamide	6	1.5%
42.	Folic acid	5	1.3 %
43.	Poly Ethylene Glycol	5	1.3 %
44.	Carvedilol	5	1.3 %
45.	Clorpheniramine	5	1.3 %

46.	Amitriptyline	5	1.3%
47.	Betastin	4	1.0%
48.	Bisacodyl	4	1.0%
49.	Azithromycin	4	1.0 %
50.	Candisartan	4	1.0%
51.	Methylprednisolone	4	1.0%
52.	Lotatadine	4	1.0%
53.	Bezafibrate	3	0.8 %
54.	Baclofen	3	0.8%
55.	Cephalexin	3	0.8%
56.	Theophylline	3	0.8%
57.	Hyoscine	3	0.8%
58.	Pantoprazole	2	0.5 %
59.	Methimazole	2	0.5 %
60.	Esomeprazole	2	0.5 %
61.	Dapagliflozine	2	0.5 %
62.	Ipratropium	2	0.5 %
63.	Al Hydroxide/Mag Hydroxide	2	0.5 %
64.	Sodium Hyaluronate	2	0.5%
65.	Nifedipine	2	0.5%
66.	Amoxicillin	2	0.5%
67.	Enoxaparin	2	0.5%
68.	Celecoxib	2	0.5%
69.	Dorzolamide	2	0.5%
70.	Sulphamethoxazole.trimethoprim	2	0.5%
71.	Acetazolamide	2	0.5%
72.	Amiodarone	2	0.5%
73.	Tamsulosin	1	0.3 %
74.	Ofloxacin	1	0.3 %
75.	Omega – 3	1	0.3 %
76.	Declofenac	1	0.3 %
77.	Medroxyprogesterone acetate	1	0.3 %
78.	Fexofenadine	1	0.3 %
79.	Feniton sod.	1	0.3 %
80.	Tamoxifen	1	0.3 %
81.	Multi vitamins	1	0.3 %
82.	5-Aminosalicylic acid	1	0.3%
83.	Methotrexate	1	0.3 %
84.	Gabapentin	1	0.3 %
85.	Cetirizine	1	0.3%
86.	Letrozole	1	0.3%
87.	Triamcinolone	1	0.3%
88.	Nimesulide	1	0.3%
89.	Miconazole	1	0.3%
90.	Orphenadrine	1	0.3%
91.	Methyldopa	1	0.3%
92.	Sacubitril	1	0.3%
93.	Levofloxacin	1	0.3%
94.	Pregabalin	1	0.3%
95.	Erythromycin	1	0.3%

96.	Lipidosterolic extract	1	0.3%
97.	Topiramate	1	0.3%
98.	Fluconazole	1	0.3%
99.	Metronidazole	1	0.3%
100.	Metoclopramide	1	0.3%
101.	Metolazone	1	0.3%
102.	Etoricoxib	1	0.3%
103.	Repaglinide	1	0.3%
104.	Propranolol	1	0.3%
105.	Cholecalciferol	1	0.3%
106.	Alfuzosin	1	0.3%
107.	Mycophenolate sod.	1	0.3%
108.	Acyclovir	1	0.3%
109.	Homatropine/paracetamol/papverine	1	0.3%
110.	Promethazine	1	0.3%
111.	Levofloxacin	1	0.3%
112.	Latanoprost	1	0.3%
113.	Lansoprazole	1	0.3%
114.	Diltiazem	1	0.3%

Appendix F

List of all potential drug-drug interactions

No.	Drug-drug interactions	Frequency	Percentage	Risk rating
1.	Acetyl salicylic acid/Metformin	246	61.5%	C
2.	Glimepiride/Metformin	162	40.5%	C
3.	Glimepiride/ASA	132	33.0%	C
4.	Metformin/Enalapril	113	28.3%	C
5.	Enalapril/ASA	97	24.3%	C
6.	Insulin/Metformin	82	20.5%	C
7.	ASA/Furosemide	82	20.5%	C
8.	Metformin/Furosemide	77	19.3%	C
9.	Atorvastatin/Carbamazepine	63	15.8%	D
10.	Glimepiride/Enalapril	58	14.5%	B
11.	Insulin/Enalapril	53	13.3%	B
12.	Insulin/Furosemide	49	12.3%	C
13.	Alfacal/Calcium	46	11.5%	C
14.	Glimepiride/Ranitidine	41	10.3%	C
15.	ASA/Calcium	41	10.3%	B
16.	Clopidogrel/Atorvastatin	39	9.8%	B
17.	ASA/Clopidogrel	37	9.3%	C
18.	Insulin/Bisoprolol	36	9.0%	C
19.	Enalapril/Furosemide	35	8.8%	C
20.	Glimepiride/Furosemide	35	8.8%	C
21.	Metformin/Hydrochlorothiazide	34	8.5%	C
22.	Glimepiride/Bisoprolol	34	8.5%	C
23.	Amlodipine/Carbamazepine	23	5.8%	D
24.	Glimepiride/Insulin	22	5.5%	C
25.	Spironolactone/Atorvastatin	20	5.0%	C
26.	Bisoprolol/Carbamazepine	20	5.0%	D
27.	ASA/Spironolactone	19	4.8%	A
28.	Amlodipine/Calcium	18	4.5%	C
29.	Glimepiride/Calcium	18	4.5%	B
30.	Ranitidine/Calcium	17	4.3%	B
31.	Carbamazepine/Allopurinol	14	3.5%	C
32.	Glimepiride/Hydrochlorothiazide	13	3.3%	C
33.	Insulin/Hydrochlorothiazide	12	3.0%	C
34.	Vildagliptin/ASA	12	3.0%	C
35.	Glimepiride/Atenolol	12	3.0%	C
36.	Losartan/Carbamazepine	12	3.0%	D
37.	Insulin/Atenolol	10	2.5%	C
38.	Enalapril/Hydrochlorothiazide	9	2.3%	C
39.	Enalapril/Sitagliptin	9	2.3%	C
40.	Clopidogrel/Amlodipine	9	2.3%	C
41.	Digoxin/Atorvastatin	9	2.3%	C
42.	Digoxin/Furosemide	9	2.3%	C
43.	Calcium/Hydrochlorothiazide	7	1.8%	C
44.	Enalapril/Spironolactone	6	1.5%	C
45.	Metformin/Ramipril	6	1.5%	C

46.	Glibenclamide/Metformin	6	1.5%	C
47.	ASA/Indomethacin	6	1.5%	D
48.	Isosorbide dinitrate/Carbamazepine	5	1.3%	D
49.	Insulin/Cortisone	5	1.3%	C
50.	Levothyroxine/Calcium	5	1.3%	D
51.	Amiloride/ASA	5	1.3%	A
52.	ASA/Ramipril	5	1.3%	C
53.	Warfarin/Glimepiride	5	1.3%	C
54.	Glibenclamide/ASA	5	1.3%	C
55.	Glimepiride/Vildagliptin	5	1.3%	D
56.	Atenolol/Bisoprolol	5	1.3%	C
57.	Carbamazepine/Hydrochlorothiazide	5	1.3%	C
58.	Atorvastatin/Carvedilol	5	1.3%	C
59.	Digoxin/Bisoprolol	5	1.3%	C
60.	Indomethacin/Enalapril	5	1.3%	C
61.	Insulin/Vildagliptin	4	1.0%	D
62.	Insulin/Timolol	4	1.0%	C
63.	Salbutamol/Bisoprolol	4	1.0%	C
64.	Spironolactone/Losartan	4	1.0%	C
65.	Digoxin/Spironolactone	4	1.0%	C
66.	Amlodipine/Indomethacin	4	1.0%	B
67.	Furosemide/Budesonide	3	0.8%	C
68.	Atenolol/Calcium	3	0.8%	B
69.	Amlodipine/Diclofenac	3	0.8%	B
70.	ASA/Diclofenac	3	0.8%	D
71.	Bisoprolol/Diclofenac	3	0.8%	C
72.	Enalapril/Losartan	3	0.8%	D
73.	Enalapril/Candesartan	3	0.8%	D
74.	Enalapril/Amiloride	3	0.8%	C
75.	Clopidogrel/Omeprazole	3	0.8%	D
76.	Vildagliptin/Furosemide	3	0.8%	C
77.	Vildagliptin/Hydrochlorothiazide	3	0.8%	C
78.	Glibenclamide/Enalapril	3	0.8%	B
79.	Metformin/Cephalexin	3	0.8%	C
80.	Amitriptyline/Carbamazepine	3	0.8%	C
81.	Digoxin/Alfacalcidol	3	0.8%	C
82.	Indomethacin/Cortisone	3	0.8%	C
83.	Glimepiride/Indomethacin	3	0.8%	B
84.	Furosemide/Diclofenac	2	0.5%	D
85.	Iron/Ranitidine	2	0.5%	C
86.	Clopidogrel/Diclofenac	2	0.5%	C
87.	Enalapril/Vildagliptin	2	0.5%	C
88.	Enalapril/Enoxaparin	2	0.5%	C
89.	Bisoprolol/Timolol	2	0.5%	C
90.	Glimepiride/Timolol	2	0.5%	C
91.	Celecoxib/Enalapril	2	0.5%	C
92.	Insulin/Levofloxacin	2	0.5%	C
93.	Glimepiride/Sulphamethoxazole+Trimethoprim	2	0.5%	C

94.	Metformin/Sulphamethoxazole+Trimethoprim	2	0.5%	C
95.	Acetazolamide/ASA	2	0.5%	D
96.	Metformin/Acetazolamide	2	0.5%	C
97.	Atorvastatin/Esomeprazole	2	0.5%	C
98.	Amiodarone/Furosemide	2	0.5%	C
99.	Atorvastatin/Amiodarone	2	0.5%	C
100.	Bisoprolol/Amiodarone	2	0.5%	C
101.	Clopidogrel/Amiodarone	2	0.5%	C
102.	Acetaminophen/Carbamazepine	2	0.5%	C
103.	Ranitidine/Carvedilol	2	0.5%	C
104.	Glimepiride/Carvedilol	2	0.5%	C
105.	Insulin/Carvedilol	2	0.5%	C
106.	Digoxin/Carvedilol	2	0.5%	C
107.	Ibuprofen/Indomethacin	2	0.5%	C
108.	ASA/Ibuprofen	2	0.5%	D
109.	Ibuprofen/Cortisone	2	0.5%	C
110.	Bisoprolol/Alfuzosin	1	0.3%	C
111.	Atorvastatin/Esomeprazole	1	0.3%	B
112.	Salbutamol/Budesonide	1	0.3%	B
113.	Budesonide/Calcium	1	0.3%	D
114.	Diclofenac/Enalapril	1	0.3%	C
115.	Atenolol/Diclofenac	1	0.3%	C
116.	Timolol/Diclofenac	1	0.3%	C
117.	Diclofenac/Losartan	1	0.3%	C
118.	glimepiride/Diclofenac	1	0.3%	B
119.	Amiloride/Losartan	1	0.3%	C
120.	Amiloride/Candesartan	1	0.3%	C
121.	Clopidogrel/Pantoprazole	1	0.3%	D
122.	Clopidogrel/Esomeprazole	1	0.3%	D
123.	Spironolactone/Candesartan	1	0.3%	C
124.	Spironolactone/Ramipril	1	0.3%	C
125.	Furosemide/Ramipril	1	0.3%	C
126.	Glimepiride/Ramipril	1	0.3%	B
127.	Glimepiride/Glibenclamide	1	0.3%	C
128.	Glibenclamide/Atenolol	1	0.3%	C
129.	Glibenclamide/Ranitidine	1	0.3%	C
130.	Glibenclamide/Insulin	1	0.3%	C
131.	Glibenclamide/Indomethacin	1	0.3%	B
132.	Bisoprolol/Nifedipine	1	0.3%	C
133.	Clopidogrel/Nifedipine	1	0.3%	C
134.	Nifedipine/Calcium	1	0.3%	C
135.	Nifedipine/Doxazocin	1	0.3%	C
136.	Sacubitril/Enalapril	1	0.3%	X
137.	Sacubitril/Amlodipine	1	0.3%	C
138.	Sacubitril/Furosemide	1	0.3%	C
139.	Sacubitril/Valsartan	1	0.3%	C
140.	Atorvastatin/Sacubitril	1	0.3%	B
141.	Celecoxib/Indomethacin	1	0.3%	X
142.	Furosemide/Celecoxib	1	0.3%	D

143.	Enoxaparin/Celecoxib	1	0.3%	C
144.	Amlodipine/Celecoxib	1	0.3%	B
145.	Levofloxacin/Celecoxib	1	0.3%	C
146.	Levofloxacin/Calcium	1	0.3%	D
147.	Levofloxacin/Enalapril	1	0.3%	B
148.	Sulphamethoxazole+Trimethoprim/ASA	1	0.3%	C
149.	Hydrochlorothiazide/Hyoscine-N-Butylbromide	1	0.3%	C
150.	Pregabalin/Carbamazepine	1	0.3%	C
151.	Pregabalin/Enalapril	1	0.3%	C
152.	Alfacalcidol/Pregabalin	1	0.3%	B
153.	Enoxaparin/ASA	1	0.3%	C
154.	Amlodipine/Erythromycin	1	0.3%	D
155.	Atorvastatin/Erythromycin	1	0.3%	C
156.	Topiramate/ASA	1	0.3%	D
157.	Topiramate/Carbamazepine	1	0.3%	D
158.	Metformin/Topiramate	1	0.3%	C
159.	Topiramate/Furosemide	1	0.3%	C
160.	Acetazolamide/Topiramate	1	0.3%	X
161.	Carbamazepine/Acetazolamide	1	0.3%	C
162.	Acetazolamide/Dorzolamide	1	0.3%	X
163.	Glimepiride/Fluconazole	1	0.3%	D
164.	Amlodipine/Fluconazole	1	0.3%	C
165.	Atorvastatin/Fluconazole	1	0.3%	C
166.	Atorvastatin/Esomeprazole	1	0.3%	C
167.	Etoricoxib/Indomethacin	1	0.3%	X
168.	Etoricoxib/ASA	1	0.3%	D
169.	Etoricoxib/Carbamazepine	1	0.3%	D
170.	Etoricoxib/Enalapril	1	0.3%	C
171.	Etoricoxib/Hydrochlorothiazide	1	0.3%	C
172.	Etoricoxib/Candesartan	1	0.3%	C
173.	Repaglinide/ASA	1	0.3%	C
174.	Repaglinide/Atorvastatin	1	0.3%	C
175.	Repaglinide/Metformin	1	0.3%	C
176.	Hydrochlorothiazide/Chlorpheniramine	1	0.3%	C
178.	Mycophenolate/Omeprazole	1	0.3%	C
179.	Azithromycin/Amitriptyline	1	0.3%	C
180.	Atorvastatin/Esomeprazole	1	0.3%	C
181.	Insulin/Dapagliflozin	1	0.3%	D
182.	Dapagliflozin/ASA	1	0.3%	C
183.	Dapagliflozin/Enalapril	1	0.3%	C
184.	Amiodarone/Enalapril	1	0.3%	C
185.	Amiodarone/Spironolactone	1	0.3%	C
186.	Sitagliptin/Amiodarone	1	0.3%	C
187.	Ranitidine/Amiodarone	1	0.3%	C
188.	Betahistine/Loratadine	1	0.3%	C
189.	Carbamazepine/Loratadine	1	0.3%	C
190.	Loratadine/Promethazine	1	0.3%	C
191.	Clopidogrel/Lansoprazole	1	0.3%	D
192.	Levothyroxine/Omeprazole	1	0.3%	B

193.	Glimepiride/Propranolol	1	0.3%	C
194.	Glimepiride/Ofloxacin	1	0.3%	C
195.	Glimepiride/Medroxyprogesterone acetate	1	0.3%	C
196.	Atenolol/Timolol	1	0.3%	C
197.	Glimepiride/Amitriptyline	1	0.3%	C
198.	Baclofen/Amitriptyline	1	0.3%	C
199.	Indomethacin/Amitriptyline	1	0.3%	C
200.	Hydrochlorothiazide/Amitriptyline	1	0.3%	C
201.	ASA/Amitriptyline	1	0.3%	C
202.	Carbamazepine/Gabapentin	1	0.3%	C
203.	Carbamazepine/Theophylline	1	0.3%	D
204.	Methotrexate/Folic acid	1	0.3%	A
205.	Digoxin/Hydrochlorothiazide	1	0.3%	C
206.	Digoxin/Omeprazole	1	0.3%	B
207.	Digoxin/Calcium	1	0.3%	C
208.	Digoxin/Colchicine	1	0.3%	C
209.	Metformin/Triamcinolone	1	0.3%	C
210.	Triamcinolone/ASA	1	0.3%	C
211.	Indomethacin/Triamcinolone	1	0.3%	C
212.	Indomethacin/Losartan	1	0.3%	C
213.	Indomethacin/Candesartan	1	0.3%	C
214.	Indomethacin/Hydrochlorothiazide	1	0.3%	C
215.	Furosemide/Indomethacin	1	0.3%	D
216.	Glimepiride/Indomethacin	1	0.3%	D
217.	Bisoprolol/Indomethacin	1	0.3%	C
218.	Spironolactone/Indomethacin	1	0.3%	C
219.	Ibuprofen/Triamcinolone	1	0.3%	C
220.	Amlodipine/Ibuprofen	1	0.3%	B
221.	Bisoprolol/Ibuprofen	1	0.3%	C
222.	Clopidogrel/Ibuprofen	1	0.3%	C
223.	Ibuprofen/Ramipril	1	0.3%	C
224.	Atorvastatin/Esomeprazole	1	0.3%	B
225.	Nimesulide/ASA	1	0.3%	D
226.	Bisoprolol/Nimesulide	1	0.3%	C
227.	Nimesulide/Losartan	1	0.3%	C
228.	Amlodipine/Nimesulide	1	0.3%	B

جامعة النجاح الوطنية

كلية الدراسات العليا

تقييم التفاعلات الدوائية المحتملة بين الادوية الموصوفة لمرضى السكري من النوع الثاني في مراكز الرعاية الصحية الأولية: دراسة مقطعية من فلسطين

إعداد

صبرين رأفت حسن عثامنة

إشراف

د. نصر شريم

قدمت هذه الاطروحة استكمالاً لمتطلبات الحصول على درجة الماجستير في الصيدلة السريرية، بكلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس – فلسطين.

2020

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الملخص

الخلفية:

في وقتنا الحاضر، هناك مخاوف صحية عالمية مرتبطة بخطر حدوث أخطاء دوائية بشكل عالي النسبة، ينسب الكثير منها الى التفاعلات الدوائية.الحالات المرضية المصاحبة مثل : مرض السكري، ارتفاع ضغط الدم، الدهنيات، امراض اكلى وأمراض الشرايين المحيطية جميعها تتطلب علاجا معقدا بادوية متعددة. وبالتالي فان اعطاء أكثر من دواء واحد بشكل متزامن هو ممارسة شائعة للتحكم في حالاتهم، ولهذا السبب، فإن مرضى الأدوية المتزامنة او ما يطلق عليهم" صيدلية متعددة" هم اكثر عرضة للتفاعلات الدوائية. في بلادنا لا توجد دراسة محلية تعنى بتقييم مدي انتشار التفاعلات الدوائية المحتملة لدى مرضى السكري من النوع الثاني، وهذا هو سبب اجراء الدراسة.

هدف الدراسة:

الهدف من هذه الدراسة هو تقييم التفاعلات الدوائية المحتملة بين الادوية الموصوفة لمرضى السكري من النوع الثاني وفحص العوامل المرتبطة بهذه التفاعلات في مراكز الرعاية الصحية الاولية.

المنهجية:

الدراسة هي عبارة عن مسح مبني على الملاحظة يستخدم تصميم مقطعي يشمل مرضى السكري من النوع الثاني، حيث زاروا مراكز الرعاية الصحية الأولية التابعة لوزارة الصحة بين شهري تموز وأيلول 2018. ويتألف حجم العينة من 400 مريض، جميعهم من الجزء الجنوبي من الضفة الغربية، الخليل وبيت لحم. تمت مراجعة ميزاتهم الديموغرافية الاجتماعية، وحالاتهم الطبية والعلاج من خلال المقابلات الموجهة بالاستبيان. تم إدخال جميع وصفات الأدوية الخاصة بهم إلى مدقق Lexi-Comp لمعرفة التفاعلات الدوائية المحتملة في أدويتهم. إلى جانب ذلك، تقييم حدة هذه التفاعلات الى ممنوع، حاد، متوسط او خفيف.

النتائج :

من بين 400 مريض، كان أقل من النصف بقليل فوق 60 عامًا، وكان معظمهم من الإناث. كانت الحالات المرضية الأكثر شيوعًا الموجودة في مرضى السكري كما يلي: 77.3% يعانون من أمراض القلب والأوعية الدموية، و64.5% يعانون من اضطراب شحميات الدم، و12.0% يعانون من النقرس. علاوة على ذلك، تم استخدام ما مجموعه 114 دواءً مختلفًا، وأكثر الأدوية الموصوفة شيوعًا هي Metformin الذي يستخدم بنسبة 85.5%، يليه Atorvastatin بنسبة 74.5%، Acetyl salicylic acid (ASA) الذي يستخدمه 74.0% من المرضى. كانت التفاعلات الأكثر شيوعًا في 61.5% من المرضى هي ASA مع Metformin يليه Glimepiride مع Metformin في 40.5% من الحالات. من بين المشاركين، كان لدى 96% من المرضى تفاعل دوائي واحد على الأقل محتمل. تم تحديد إجمالي 2627 تفاعلًا، بمتوسط 6 تفاعلات لكل وصفة طبية. وفقًا لتصنيف المخاطر، كانت 1.33% هي A، 11.72% هي B، 76.67% هي C، 10.01% هي D، 0.27% هي X. كان عدد التفاعلات الدوائية المحتملة للمرضى مرتبطًا أيضًا بعمرهم ومستواهم التعليمي وأمراضهم المصاحبة وعدد الأدوية الموصوفة والمضاعفات (قيمة p <0.05 لكل واحد). ومع ذلك، لم تكن هناك علاقة ذات دلالة إحصائية مع الجنس أو الحالة المادية أو التدخين (قيمة p> 0.05).

الخلاصة:

كان انتشار التفاعلات الدوائية بين الأدوية الموصوفة لمرضى السكري من النوع الثاني شائعًا جدًا. تتزايد هذه الاحتمالية بالتوازي مع زيادة عدد الأدوية، والأمراض المصاحبة، بالإضافة إلى وجود مضاعفات. يمكن أن يؤدي تحديث البيانات المتعلقة بالتفاعلات الدوائية مع التواصل الجيد والفعال بين مقدمي الرعاية الصحية، وخاصة الواصفين للأدوية والصارفين لها، دورًا مهمًا في تقليل التفاعلات الدوائية.

الكلمات المفتاحية:

التداخلات الدوائية، داء السكري، تعدد الأدوية، الوصفات الطبية، فلسطين.