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Incidence of potential drug-drug interactions with antidiabetic drugs

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In an effort to achieve normoglycemia more than one antidiabetic agent is usually needed. Diabetes is associated with several comorbidities and patients with diabetes are often treated with multiple medications. Therefore, patients with diabetes are especially exposed to drug-drug interactions (DDIs). The aim of this study was to analyse the incidence and type of potential DDIs of antidiabetic drugs in patients with diabetes. This retrospective study analyzed pharmacy record data of 225 patients with diabetes mellitus. Both type 1 and type 2 diabetic patients who were taking at least one antidiabetic agent during the period of six months were included. We investigated associated therapy in that period in order to identify potential DDIs with antidiabetic therapy. Potential interactions were identified by Lexicomp® Lexi-Interact™ Online (Lexi-Comp, Inc., Hudson, USA) software which categorizes potential DDIs according to clinical significance in five types (A, B, C, D and X). Categories C, D and X are of clinical concern and always require medical attention (therapy monitoring, therapy modification or avoiding combination). We found that 80.9% of patients had at least one potential category C interaction while there were no D and X interactions. Most frequently encountered potential DDI (n = 176) included antidiabetic drugs and thiazide or thiazide like diuretics. Patients with diabetes are exposed to a large number of potential clinically significant DDIs that may require appropriate monitoring. Using databases of DDIs could be helpful in reducing the risk of potential clinically significant DDIs.

1. Introduction

Diabetes is a chronic metabolic disease which is characterized by absolute or relative insulin deficiency which leads to hyperglycemia. It is an important public health problem because it causes early cardiovascular morbidity and mortality. Half of patients with diabetes die from cardiovascular diseases, especially from myocardial infarction and stroke (Morrish et al. 2001). The estimated number of patients with some form of diabetes mellitus is 347 million worldwide (Danaei et al. 2011). It is expected that prevalence will increase to approximately 550 million by 2030 (Whiting et al. 2011). According to the Croatian national registry there were 234.457 adults suffering from diabetes in Croatia in 2012; 6.0% had diabetes mellitus type 1 and 93.0% had diabetes type 2. Among adults with diagnosed diabetes in Croatia 24.7% take insulin only, 20.7% take both insulin and oral medications, 53.1% take only oral medications and 1.5% are treating diabetes with basic diet measures (Poljicanin et al. 2012). Antihyperglycemic agents include insulin, sulphonylureas, biguanides, α-glucosidase inhibitors, meglitinide analogs, thiazolidinediones, dipeptidyl peptidase-4 inhibitors and incretin mimetics. According to the Agency for Medicinal Products and Medical Devices of Croatia in 2012, antidiabetics were the fifth most commonly used drugs in Croatia (Agency 2014). In an effort to achieve normoglycemia, more than one antidiabetic agents is usually needed. Diabetes is associated with different comorbidities and patients with diabetes are often treated with multiple medications. It is known that the risk of an adverse event due to drug-drug interactions (DDIs) is substantially increased when multiple drugs are taken (Juurlink et al. 2003). Therefore, patients with diabetes are especially exposed to DDIs. Most of the evidence is derived from case reports or investigations of potential DDIs in patients from hospitals or pharmacies (Peterson and Bates 2001; Halkin et al. 2001; Bacic Vrca et al. 2010; Schorr et al. 2014). DDIs can be a serious threat to public health. It is important to frequently observe DDIs in current pharmacotherapy because the prediction of DDIs is of clinical importance for selecting regimens and adjusting doses (Pirmohamed et al. 2004). Likewise, knowledge of DDIs is an important parameter for rational pharmacotherapy (Bacic Vrca et al. 2005). We sought to investigate the incidence of potential DDIs including antidiabetic agents in patients with diabetes using records of a community pharmacy.

2. Investigations, results and discussion

We have analyzed pharmacy record data and all patient visits to the pharmacy in a two month period to identify patients with antidiabetic therapy. This retrospective study analyzed 225 patients with diabetes mellitus from community pharmacy record data with consecutive processing. Patients were identified by ICD codes listed in their pharmacy data records. The study included patients with both type 1 and type 2 diabetes who have been dispensed with at least one antidiabetic agent during six months. Only patients who have regularly collected their prescriptions and were regularly dispensed with their medication in

Table 1: Demographic data and drug-drug interations

	All patients (n = 225)	
Age (y), mean ([a]SD)	65.97 (11.7)	
range	20-92	
Gender, n (%)		
Men	108 (48.0)	
Women	117 (52.0)	
Type of [b]DM, n (%)		
Type I	14 (6.3)	
Type II	211 (93.7)	
Antidiabetic drug prescribed per patient (mean, range)	1.73 (1-5)	
Other prescribed drugs per patient (mean, range)	5.17 (0-17)	
Interactions, n (mean)	623 (2.8)	Patients, n (%)
[c]A, n (%)	2 (0.3)	2 (0.9)
[d]B, n (%)	164 (26.3)	109 (48.4)
[e]C, n (%)	457 (73.4)	182 (80.9)
[f]D, n (%)	0 (0)	0
[g]X, n (%)	0 (0)	0

Abbreviations: [a]SD - standard deviation; [b]DM - diabetes mellitus; [c]A - no known interaction; [d]B - no action needed; [e]C - monitor therapy; [f]D - consider therapy modification [g]X - avoid combination.

six month time-period were eligible for inclusion in this study. We have analyzed patients' therapy cards which are kept in the pharmacy in order to identify potential DDIs involving antidiabetic agents and other co-prescribed medication. We decided to exclude over the counter medication in the analysis as they are considered to be safer for wide use and have a lower risk of potential DDIs.

Fifty-two percent of patients enrolled in this study were women. The mean age of study participants was 66 (range: 20-92). The proportion of patients included in the study with diabetes type 1 (ICD code E10) (6.3%) and diabetes type 2 (ICD code E11) (93.7%) correlated with their proportion in the Croatian national registry of diabetic patients (Poljicanin et al. 2012). The average number of prescribed antidiabetic agents was 1.7 and the average number of other prescribed drugs was 5.2. We identified 623 potential DDIs and 73.4% of them were considered clinical significant - C type interactions by Lexi-Interact™ software (Lexi-Comp 2014). On the other hand, there were no D and X interactions which imply therapy modification. More than 4/5 (80.9%) of patients had at least one C interaction (Table 1). Most frequently prescribed antidiabetic drugs in all patients were metformin, glimepiride and gliclazide; 146 (64.9%), 56 (24.9%) and 40 (17.8%), respectively. Glimepiride, although used in only 24.9% of patients, had the highest number of potential DDI; almost twice as metformin which was prescribed to 64.9% of patients. Glyburide showed the greatest potential for the development of potential DDI since it was used by 26 patients and had 81 potential interactions. Among these, 50 interactions were of clinical concern. For three patients gliquidone has been dispensed, a drug not recognized in the Lexicomp program, and thus, no interactions for gliquidone could be noted. Prescribing information on gliquidone implies that certain drugs which were prescribed in our study population might interfere with gliquidone and enhance (NSAID, ACE inhibitors, beta-blockers) or reduce (levothyroxine, thiazide diuretics, loop diuretics) its hypoglycemic effect (Glurenorm 2012). It is known that gliquidone metabolism is mainly mediated by the CYP3A4 enzyme. Therefore, inhibitors and inducers of this enzyme could cause a significant interaction with gliquidone (He et al. 2014). Newer antidiabetics (dipeptidyl peptidase-4 inhibitors and incretin mimetics) were rarely prescribed. Sitagliptin has been used in only 13.8% of patients while incretin mimetics were not identified in any pharmacotherapy card despite the fact that they are present for some time on the Croatian market (Table 2).

Most commonly prescribed co-medications were angiotensin-converting enzyme inhibitors - ACEI (53.7%), mostly ramipril. Other classes of co-prescribed drugs frequently used were as follows: statins (50.2%), thiazide or thiazide-like diuretics (46.2%), beta-blockers (38.2%), calcium channel blockers (31.5%), anxiolytics (28.4%) and nonsteroidal antiinflammatory drugs - NSAIDs (24.4%). Other classes of co-administered drugs and their prevalence are listed in Table 3. Most encountered antidiabetics' DDI was associated with thiazide and thiazide like diuretics (176 interactions). Other potentially relevant DDIs are listed in Table 4. Only 37 patients (16.4%) were taking insulin. Those patients had more antidiabetic drugs in their therapy, however, not statistically significant (tested by Student's t-test). On the other hand, they did have significantly more DDIs compared with patients who did not have insulin in therapy tested by Student's t-test (Table 5). Older patients ($\geq$65 y vs < 65 y; n = 122 vs n = 103) have been prescribed fewer antidiabetic drugs (1.65 vs 1.86; p = ns) but a significantly higher number of other medications (5.51 vs 4.56; p = 0.02). We found no difference in DDIs involving antidiabetics in regards to patients' age or gender (Table 6).

Antidiabetic drug interactions have been vastly investigated (Freeman et al. 2012; Munger 2010; Scheen 2005; Rathmann et al. 2003). We showed that a very large proportion of patients with diabetes mellitus (80.9%) had at least one potential, clinically significant DDI that requires monitoring of therapy (category C). Despite the fact that patients had on average 1.73 antidiabetic drugs and 5.17 other drugs prescribed we did not found DDIs of D and X category. The absence of these DDIs could be a result of unfrequent prescription of certain drugs that could cause D and X category DDI with antidiabetic agents and/or prescribers' awareness of their significance and potential to cause DDI with antidiabetics. Nevertheless, community pharmacists must be aware of potential interactions of co-prescribed drugs. All strong CYP2C9 inhibitors (fluorouracil, gemfibrozil, nicardipine) and inducers (carbamazepine, phenytoin, rifampin) in combination with sulfonylurea derivatives comprise potential D category DDI (Lexi-Comp 2014). Somatropin might cause a D category DDI with all antidiabetic agents (20). Gemfibrozil might increase the serum concentration of repaglinide eight-fold and prolong its half-time making this drug combina-

Table 2: Proportion of prescribed antidiabetic drugs and drug-drug interactions

			Interactions					
Prescribed antidiabetic drug	[a]ATC code	Patients, n (%)	A	B	C	D	X	Total
Metformin	A10BA02	146 (64.9)	0	0	84	0	0	84
Glimepiride	A10BB12	56 (24.9)	0	53	111	0	0	164
Gliclazide	A10BB09	40 (17.8)	0	38	72	0	0	110
Insulin	A10A	37 (16.4)	0	22	79	0	0	101
Sitagliptine	A10BH01	31 (13.8)	0	1	75	0	0	76
Glyburide	A10BB01	26 (11.6)	0	31	50	0	0	81
Acarbose	A10BF01	16 (7.11)	0	0	23	0	0	23
Repaglinide	A10BX02	11 (4.9)	2	8	20	0	0	30
Pioglitazone	A10BG03	3 (1.3)	0	0	8	0	0	8
Gliquidone	A10BB08	3 (1.3)	[b]NA	NA	NA	NA	NA	NA
Vildagliptine	A10BH02	1 (0.4)	0	0	1	0	0	1

Abbreviations: [a]ATC - anatomical therapeutic chemical classification; [b]NA - not available

Table 3: Other classes of prescribed drugs

Prescribed drug class	[b]ATC code	Patients, n (%)
[a]ACE inhibitors	C09A	121 (53.7)
Statins	C10AA	113 (50.2)
Thiazide and thiazide like diuretics	C03AA03, C03BA	104 (46.2)
Beta blockers	C07A	86 (38.2)
Calcium channel blockers	C08CA	71 (31.5)
Anxiolytics	N05B	64 (28.4)
[c]NSAIDs	M01A	55 (24.4)
[d]ARBs	C09CA	39 (17.3)
Antibiotics	J01A, J01C, J01D, J01F, J01G	28 (12.4)
[e]PPIs	A02BC	28 (12.4)
Narcoanalgetics	N02AX	25 (11.1)
Nitrates	C01DA	25 (11.1)
Bronchospasmolytics and antiasthmatics	R03	23 (10.2)
Loop diuretics	C03CA	18 (8.0)
Antiallergics	R06	18 (8.0)
Fenofibrate	C10AB05	17 (7.5)
Levotyroxine	H03AA01	16 (7.1)
Analgo-Antipiretics	N02B	16 (7.1)
Alpha blockers	C02CA	15 (6.6)
Other antihypertensive drugs	C02	15 (6.6)
H2-antagonists	A02BA	15 (6.6)
Antidepressives	N06A	14 (6.2)
Potassium compounds	A12BA	13 (5.7)
Hypnotics	N05C	13 (5.7)
Warfarin	B01AA03	11 (4.8)
Allopurinol	M04AA01	10 (4.4)
Verapamil	C08DA01	9 (4.0)
Clopidogrel	B01AC04	7 (3.1)
Antimicrobials	J01E, J01M, J01X	7 (3.1)
Other		(%) < 3

Abbreviations: [a]ACE – angiotensin converting enzyme; [b]ATC - anatomical therapeutic chemical classification; [c]NSAID – non steroid antiinflammatory drug; [d]ARB – angiotensin receptor blocker; [e]PPI – protein pump inhibitor.

tion undesirable (Niemi et al. 2003). Thus this combination of drugs should be avoided. Glyburide and bosentan, an endothelin receptor antagonist, enhance the metabolism of each other. Glyburide might enhance the hepatotoxic effect of bosentan (Lexi-Comp 2014). Therefore, this combination of drugs is contraindicated. The most commonly drugs used along with antidiabetics were antihypertensives and statins. Hypertension and dyslipidemia are common comorbidities in patients with diabetes and combination therapy is necessary to reduce the risk of cardiovascular diseases (Gaede et al. 2008). We found that ACEIs were the most commonly co-prescribed drugs. Activation of the renin-angiotensin-aldosterone system plays an important role in increasing microvascular and macrovascular complications in patients with diabetes, hypertension or other cardiovascular diseases such as chronic heart failure (CHF). ACEIs are potent antihypertensive agents but there is data indicating that they also have a specific protective effect on kidneys, heart, eyes and peripheral nerve function in patients with diabetes (Cordonnier et al. 2001). Thiazide diuretics and beta blockers were also commonly prescribed in the study population (Table 3). It is well established that the use of thiazides and beta-blockers is associated with an increased risk of developing type 2

Table 4: Most frequent drug-drug interactions with antidiabetics

Drug class	n	Interaction	n	Category	Effect
Thiazide and thiazide like diuretics	176	metformin – [e]HCTZ	43	[d]C	Thiazide diuretics may diminish the therapeutic effect of metformin
[a]ACE inhibitors	125	glimepiride - ramipril	16	[c]B	ACE inhibitors may enhance the hypoglycemic effect of sulfonylureas
Antidiabetics	93	glimepiride – sitagliptin	20	C	Hypoglycemic agents may enhance the adverse/toxic effect of other hypoglycemic agents
Beta blockers	65	glimepiride - bisoprolol	14	C	Beta-blockers may enhance the hypoglycemic effect of sulfonylureas
[f]NSAIDs	44	glimepiride - ibuprofen	11	B	NSAID may diminish/enchance the hypoglycemic effect of sulfonylureas
Statins	26	sitagliptin - atorvastatin	8	B	Atorvastatin may increase the serum concentration of sitagliptin
Loop diuretics	23	glimepiride - furosemide	5	B	Loop diuretics may diminish the hypoglycemic effect of hypoglycemic agents
[b]ARBs	11	glimepiride - losartan	4	C	Losartan may decrease the metabolism of sulfonylureas
Antibiotics	9	glimepiride - ciprofloxacin	2	C	Quinolone antibiotics may enhance/diminish the hypoglycemic effect of sulfonylureas

Abbreviations: [a]ACE – angiotensin converting enzyme; [b]ARBs – angiotensin receptor blockers; [c]B - no action needed; [d]C - monitor therapy; [e]HCTZ - hydrochlorothiazide; [f]NSAID – nonsteroidal anti-inflammatory drugs

diabetes, compared with treatment with calcium channel blockers and inhibitors of the renin-angiotensin-aldosterone system (Reboldi et al. 2009). However, it is unknown whether treatment with beta-blockers and/or thiazide diuretics in patients with established diabetes type 2 lead to any metabolic adverse events of clinical importance (Ryden et al. 2013). Negative metabolic effects may be less important than treating hypertension in patients with diabetes, at least in regards to macrovascular complication development (UK Prospective Diabetes Study Group 1998a; UK Prospective Diabetes Study Group 1998b). Some studies have shown that thiazide or thiazide like diuretics are superior to ACE inhibitors and calcium-channel blockers in preventing one or more major forms of cardiovascular disease in high-risk patients with hypertension and in patients with hypertension and diabetes (ALLHAT 2002). Results of meta-analysis suggest that regulation of blood pressure should be a priority compared to the selection of drugs (Turnbull et al. 2005).

Statin therapy improves the lipid profile and is usually recommended for patients with diabetes. Some studies, however, suggest that there is an increased incidence of diabetes in patients treated with statins (Sattar et al. 2010). Withdrawal of statins in patients with newly diagnosed diabetes and who already have diabetes is not recommended, however (Ravi et al. 2012).

The most frequently prescribed antidiabetic drug was metformin. According to contemporary guidelines, metformin is the first-line treatment of type 2 diabetes (Inzucchi et al. 2012). Metformin is an insulin sensitizer and is generally well tolerated. The most significant side effect is lactic acidosis. The elimination of metformin is dependent on the renal function. So, drugs impairing the renal function can cause accumulation of metformin and increase the risk of lactic acidosis. Some of the medicines increase the possibility of the occurrence of lactic acidosis such as: loop diuretics, ACEIs, NSAIDs, cyclosporine, aminoglycosides or X-ray contrast media (Tornio et al. 2012). However, lactic acidosis occurs very rare in practice, probably because of adherence to the exclusion criteria for metformin treatment (Bailey and Turner 1996).

Most frequent potential DDI which we have encountered with antidiabetics in general involved thiazide and thiazide like diuretics. The most common potential DDI was that between metformin and hydrochlorothiazide. Patients with hypertension or CHF associated with diabetes are usually treated with more than one antihypertensive agent, which often include thiazides (Mogensen 2003). Thiazide diuretics may diminish the therapeutic effect of antidiabetic agents. The specific mechanism for the negative metabolic effects of the thiazides is not sufficiently clarified but data suggest that thiazides may impair insulin sensitivity, increase insulin resistance, increase basal insulin concentrations and increase plasma glucose concentrations (Salvetti and Ghiadoni 2006). In order to minimize potential adverse metabolic effects it is better to start thiazide therapy with the lowest possible dose (Salvetti and Ghiadoni 2006; Weir et al. 1996; Neutel 1996). Other commonly identified clinically significant DDIs included glimepiride and all of them showed the potential to cause hypoglycemia except the combination with ciprofloxacin where both glucose abnormality, hypoglycemia and hyperglycemia are possible (Table 4). However, it seems that hyperglycemia associated with quinolones appears to be much more frequent than hypoglycemia (Lodise et al. 2007; Mohr et al. 2005). Data from other studies showed that hypoglycemia usually occurs within 1-2 days of initiating quinolone therapy while hyperglycemia tends to occur later in therapy (Lodise et al. 2007; Graumlich et. al 2005). The exact mechanism by which sulfonylureas interact with quinolones to promote these effects is controversial, but at least one *in vitro* study has shown that sulfonylureas enhance the insulin-secreting effects of gatifloxacin (Yamada et al. 2006). Combination of sitagliptin and glimepiride can result in adverse/toxic effects of these hypoglycemic agents even though such a combination is sometimes used intentionally to achieve a synergistic effect on glucose level control (Sheen 2010). Interaction between glimepiride and bisoprolol was also frequently seen in this study. Beta-blockers may enhance the hypoglycemic effect of sulfonylureas. All beta-blockers can mask tachycardia as an initial symptom of hypoglycemia (Fonseca 2010). If treatment requires the application of beta-blockers along with glimepiride, it is advisable to choose cardioselective beta-blockers such as bisoprolol or metoprolol as they may be safer for diabetic patients than nonselective beta-blockers (Cruickshank 2002). The interaction between glimepiride and the ARB losartan is most likely mediated by the cytochrome P450 isoenzyme CYP2C9. Losartan is a CYP2C9 inhibitor wherefore concentrations of glimepiride may be increased lead-

ing to hypoglycemia (Bjornsson 2003). In the metabolism of antidiabetic drugs, the following enzymes have the most important role: CYP2C8, 2C9 and 3A4 (Tornio et al. 2010). Recently, studies have also been focused on the role of transport proteins in the development of DDIs (Giacomini et al. 2010; Klatt et al. 2011). Therefore, all inhibitors and inducers of enzymes and transporters involved in the metabolism of antidiabetics should be observed as potential drugs that can cause interactions.

Patients who are taking insulin are considered to have a more severe stage of diabetes and in those patients who had diabetes type 2, disease can no longer be controlled with oral antidiabetic agents alone. Accordingly, those patients usually have more complications and comorbidities that require drug treatment. In order to achieve a better glucose control, it is often necessary to use more antidiabetics because it is well known that good glucose level control delays the onset or further development of complications and comorbidities. Probably due to the severity of the condition those patients had a higher number of antidiabetics and other drugs in their therapy which resulted in significantly more potential DDIs in patients on insulin ($p = 0.04$) compared to patients who did not use insulin. Elderly patients ($\geq$65y) used less antidiabetic drugs in therapy but they had significantly more other medications prescribed ($p = 0.02$). Glycemic level control in elderly people with long-standing or more complicated stage of disease should be less strict than in younger and healthier individuals (Ismail-Beigi et al. 2011). Elderly patients are at an increased risk of hypoglycemia and therefore, therapy with antidiabetic drugs requires more caution. Because of hypoglycemia and reduced physiological function, ideal HbA_{1c} values are often difficult to achieve. Thus, if target HbA_{1c} levels cannot be easily achieved, an HbA_{1c} level of 7.5–8.0% may be acceptable, transitioning upwards as age and capacity for self-care increase and cognitive, psychological, economic status and support systems deteriorate (Inzucchi et al. 2012). On the other hand, in elderly patients, complications and comorbidities are more often present and require the application of a higher number of other medications. In our study, younger patients had more antidiabetics but less other drugs, and this could explain why there was no difference in the number of potential interactions with respect to age. The total number of prescribed drugs influenced the number of potential DDIs in patients with diabetes.

3. Experimental

The study included outpatients who visited community pharmacy with prescriptions for at least one antidiabetic agent over a six-month period. Identification of patients' diagnose and concomitant therapy was made through the pharmacy record data. Potential DDIs were identified using Lexi-Interact software which categorizes each potential interaction according to clinical significance in five groups: (A) no known interaction; (B) specified agents may interact, but there is little or no evidence for clinical concern; (C) the specified agents may interact in clinically significant manner and monitoring of therapy is suggested; (D) the two medications may interact in clinically significant manner and modification of therapy is suggested; (X) contraindicated combination. Categories C, D and X are of clinical concern because they require specific actions (Lexi-Comp 2014).

Standard descriptive statistical analysis was used to describe the study population, drug utilization and potential DDIs. The median and standard deviations were calculated for continuous variables. Proportions were calculated for categorical variables. Differences in prescribed drugs and DDIs in regards to patient age, gender and insulin use were tested with Student t-test. Statistical significance was set at $p \leq 0.05$. Statistical analysis was performed using SPSS software version 21 (IBM Corporation, USA).

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