The combination of angiotensin converting enzyme inhibitors, diuretics and non-steroidal anti-inflammatory drugs in the routine community pharmacy settings in Poland: The unrecognized problem of 'Triple Whammy'. A pilot analysis.

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Abstract

Background: 'Triple Whammy' defined as a combination of angiotensin converting enzyme inhibitors/angiotensin receptor antagonist, diuretics and non-steroidal anti-inflammatory drugs remains an important clinical problem, particularly in patients with risk of renal impairment. Community pharmacy settings are considered to be an appropriate place for detection and solving of this drug-related problem.

Objectives: To estimate the frequency of 'Triple Whammy' in a routine community pharmacy setting in Poland by analysis of data obtained from refilled prescriptions.

Methods: We conducted anon-interventional, observational retrospective study to assess the rate of 'Triple Whammy" cases in a community pharmacy setting in Poland. We reviewed 14243 prescriptions to find 'Triple Whammy' cases. The analyzed prescriptions were refilled between the 1.01.2016 and 31.05.2016 in one single community pharmacy in Poland.

Results: The average age of all patients identified with 'Triple Whammy' was 68 (range, 56-91). We identified 12 prescriptions with 'Triple Whammy' among all cases, receiving most frequently ramipril (n=8 patients), diclofenac (n=6) and ketoprofen (n=5). Moreover, other medications that were prescribed to patients during the study analysis time period included proton pump inhibitors such as pantoprazole (n=3) and omeprazole (n=2), opioid analgesics – tramadol (n=1) in the fixed-dose combination with paracetamol, and one antihyperglycemic medication – metformin (n=1).

Conclusions: 'Triple Whammy' should be considered as a potential drug-related problem in Poland. Our study suggests that geriatric population is particularly affected by this drug-related problem, and, consequently, pharmaceutical care is predominantly necessary among this cohort.

Introduction

One of the most significant, yet, insufficiently described drug related problem in literature, is 'Triple Whammy' (TW). 'Triple Whammy' defined as a combination of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor antagonist (ARB) with a diuretic and non-steroidal anti-inflammatory drugs (NSAIDs). Most of the above-mentioned drugs are used in the treatment of hypertension. The monotherapy is effective only in a limited number of cases, thus recommendations and guidelines suggest polytherapy as a potential way of improving outcomes. It is not surprising that to achieve higher adherence experts recommend fixed-dose combinations, which for purpose of this introduction, should be understood as a combination of two or more antihypertensive active ingredients. On the other hand, NSAIDs are, beyond any reasonable doubts, one of the most widely used in the modern medicine which might be associated with the fact that many substances from this group are available as over-the-counter drugs. Keeping in mind that self-medication is promoted as a way of improving patients' health literacy we can assume that the use of NSAIDs will increase in the nearest future. The full list of indications in which these drugs are used is beyond the scope of this paper.[1-4]

The combination of agents mentioned above is particularly dangerous for patients diagnosed with renal failure and for elderly population.[3,4] Moreover, interactions between these drugs lead to a reduction of hypotensive effects and decrease the beneficial impact of ACEI on prognosis in heart failure.[5,6] It is important to underline that 'Triple Whammy' remains a complex phenomenon. First of all, it includes drugs from different three/four heterogeneous therapeutic classes. For instance on the one hand, under some circumstances loop diuretics can have a renoprotective effect, on the other hand, thiazide and thiazide-like diuretics lead to deterioration of renal function. So in that sense, different diuretics can have different impact on risk associated with the 'Triple Whammy'.[7] It should be stressed that the 'Triple Whammy' is a completely unexplored phenomenon in the countries where the pharmaceutical care is not well-established and the role of pharmacists is limited to dispensing the medications.

Despite the fact that the role of pharmacy practice in Poland is chiefly limited to dispensation, still, pharmacists can detect potential drug-related problems (e.g. 'Triple Whammy') in some cases. However, it is worth mentioning here that without full access to medical records, pharmacists can only predict potential problems and full confirmation should be provided by physicians after medical examination. Moreover, the lack of pharmaceutical staff may deteriorate the pace of introducing new, more clinical services into routine settings in community pharmacies. Undoubtedly, all these factors contribute to a rather theoretical chance of detection 'Triple Whammy' by pharma-

cists than a real opportunity and well-established standard of patient care.

The aim of this pilot study is to estimate the frequency of 'Triple Whammy' in the routine community pharmacy subsets. We believe that the perspective of clinical practice in Poland, where pharmaceutical care is still underscored, will be considered as an important voice in the global discussions about the safety of pharmacotherapy.[8] Moreover, we believe that our research promotes the necessity of cooperation between physicians and pharmacists to avoid prescription errors and may increase awareness of 'Triple Whammy' among healthcare professionals to ultimately improvement of patient safety.

Methods

A non-interventional and protocol-based study, with observational and retrospective character was conducted. Firstly, we analyzed 14 243 consecutive prescriptions to find 'Triple Whammy'. The analyzed prescriptions were refilled between the 1.01.2016 and 31.05.2016 and contained all drugs categories authorized by Polish law i.e.psychotropic medications and narcotics were also included. The research material was the medical documentation in the form of medical prescriptions of products of three categories of accessibility, i.e. dispensed on a doctor's prescription (Polish abbreviation – Rp.), dispensed on a doctor's prescription and containing narcotic drugs or psychotropic substances (Polish abbreviation – Rpw.) and dispensed on a doctor's prescription for restricted use (Polish abbreviation – Rpz.).

The potential 'Triple Whammy' was identified independently by two researchers. The following factors were evaluated during the research procedure: the trade and international drug name, formulation and dosage form. On the other hand, we considered the age as a patient-related factor.

The study was conducted in a single community pharmacy in central Poland. The selected community pharmacy provides a full range of pharmaceutical services authorized by the Polish pharmaceutical law and is opened 24 hours a day, 7 days a week. Moreover, it should be stressed that currently the pharmacy employs 6 pharmacists, 2 technicians and 2 additional staff members which fulfill the pharmaceutical law requirements.

The study was approved by the Ethics Committee at the Collegium Medicum in Bydgoszcz (the Nicolaus University located in Torun, Poland).

Results

We identified 12 cases of 'Triple Whammy' phenomenon among the analyzed prescriptions. The average age of all patients identified with 'Triple Whammy' was 68 years old. The youngest patient was 56 years old, and the oldest 91. The most frequently identified ACE inhibitor was ramipril (n=8 patients). Among diuretics the most commonly dispensed drug was indapamide (n=6), however, almost half of the drug-related problems were associated with using the hydrochlorothiazide (n=4). Beta-blockers were less frequently identified, only three patients have used this type of drugs and accordingly, mostly bisoprolol (n=2). Calcium channel blocker was presented only by amlodipine (n=5). Two patients were taking statins (simvastatin; n=2) and one individual used angiotensin II receptor antagonist represented by losartan (n=1). The most frequently used NSAIDs were diclofenac (n=6) and ketoprofen (n=5). From the different type of therapeutic groups, among others, we identified proton pump inhibitor - pantoprazole (n=3), opioid analgesics – tramadol (n=1) in the fixed-dose combination with paracetamol, as well as antihyperglycemic agents – metformin (n=1).

In all cases in which we identified the drug-related problem associated with simultaneous usage of NSAIDs with ACE inhibitors and diuretics, we discussed the potential clinical implications associated with the higher frequency of adverse events and harm directly related to drug-drug interactions. We summarized our results in Table 1 and in Supplementary File 1.

Discussion

To the best of our knowledge this is the first study to evaluate the scale of 'Triple Whammy' in a country where the pharmaceutical care is not well-established and the role of the pharmacists in the healthcare system is limited to dispensing medicines.

So far the 'Triple Whammy' has been evaluated in the various types of research and the association between the prevalence of this combination and adverse events has been proved several times, particularly in the context of renal failure and an impact on efficacy of hypertensive agents.[9,10] However, in contrast with our study most of conducted researches were based on cross-sectional approach or the data was derived from database.[5,11] By analyzing the data derived from prescriptions, we were able to gain novel and insightful access to real prescription patterns used by Polish prescribers.

If the above-mentioned combination is identified, the pharmacotherapy patterns should be critically revised. Under

current regulations, deprescribing remains an example of a useful tool in the process of optimizing medication use. As a matter of fact, all such patients should be carefully monitored in terms of regular blood pressure and electrolytes control.

Surprisingly, in our study, only limited number of patients used the most frequently prescribed statins such as atorvastatin and rosuvastatin, which is in contrast with the current guidelines and recommended therapy.[12] However, this might be associated with the fact that underprescribing of statins in community patients in Poland remains frequently identified the problem and should be considered as one of the aims for further evaluations. In the previous studies, underprescribing of statins has been detected among some cohorts.[13]

The low rate of identified drug-related problems in our research is in contrast with previous research in the field. Gustafsonn et al identified that 41.3% of acute hospital admissions might be associated with drug-related issues.[14] Also, de Costa et al recognized 2109 drug-related problems among 126 elderly patients taking 1332 medicinal product. [15] However, we should emphasize that our research was aimed only at searching 'Triple Whammy' and, due to this special searching criteria, the number of drug-related problems might be underestimated.

'Triple Whammy' is particularly important in the perspective of elderly cohorts, because of the prevalence of polypharmacy phenomenon among these patients.[2] In our study we found potential drug-related problems among patients who are over 65 years old. It should be stressed that among the elderly patients, drug-related problems are particularly important, because of different drug metabolism pathways and greater risk associated with adverse events, compared to different patient populations [16]. Since polypharmacy remains a predominant concern in the elderly, this patient cohort should be considered an important target for pharmaceutical care.[17]

Our findings are consistent with various types of research such as retrospective analyses, prospective studies or ‚both physicians' and pharmacists', interventions aimed at finding appropriate solutions to drug-related problems and improving the patient safety.[18]

Finally, one more aspect should be briefly discussed. Polish patients can obtain prescriptions for Rx medicinal products from family doctors, specialists in the various medical fields and, recently, also from qualified nurses who achieved certain postgraduate qualifications. Thus, the knowledge and experience of prescribers may differ significantly which leads sometimes to drug-related problems, e.g. prescribing the same active ingredient in the different brand products. Moreover, the sophistication of reimbursement rules in Poland leads to the situation in which pharmacists are mostly devoted to administrative procedures e.g. checking the correctness of prescriptions in the terms of refill date, dosage or recommended format. Less attention is paid to clinical-related issues, like detection of drug-related problems. All these factors undoubtedly affect the level of clinical services in the community pharmacies.

Our research has several important limitations. Firstly, we analyzed the data from one selected community pharmacy in Poland and the results should not be generalized to the whole country. Moreover, we have no access to medical records and documentations. We should notice that the combination of NSAIDs with ACEI or diuretics in the case of an individualized patient might be acceptable pharmacotherapy and risk-benefit ratio is more favorable. Moreover, it should be stressed that many of the identified problems are not included in the current guidelines provided by the European Society of Cardiology and partially due to this fact the awareness about drug-related problems among physicians remains insufficient. However, once more, we would like to stress that our study should be understood as a pilot and a first step towards more advanced research in the scope. Finally, we have no information about over-the-counters drugs (OTC) used by patients during the data collection period which is important as many of NSAIDs are included in this category and might be dispensed without the prescription. To sum up, further studies are warranted to estimate the real prevalence of "Triple Whammy" in routine settings, and this paper should be considered as important, although still the first voice in the discussion about the above-mentioned problem. To provide more practical recommendations, more sophisticated studies need to be implemented.

Conclusions

'Triple Whammy' is an identified phenomenon in the Polish community pharmacies. Moreover, our study suggests that geriatric population is particularly affected by this drug-related problem, and, consequently, pharmaceutical care is predominantly necessary among this cohort. Our research should be understood as a pilot of further research. Further studies may focus on investigating relationship between adherence-related issues and occurrence of Triple Whammy as one of the drug-related problems which are associated with high risk of adverse events influencing quality use of medicines.[19] Currently, in Poland, we observe a tendency to expand the pharmacists' role in the healthcare in the context of implementing new pharmaceutical services aimed at optimizing pharmacotherapy. Therefore we are sure that community pharmacies settings are suitable to detect drug-related problems. Finally, we believe that screening prescriptions, even without full access to medical records, might be an effective way of optimizing the pharmacotherapy.

Table 1. Active pharmaceutical ingredients among identified Triple Whammy cases.

Therapeutic group	International Drug Name	Number of patients
Non-steroidal anti-inflammatory drug	Diclofenac	6
	Ketoprofen	5
	Meloxicam	1
ACE inhibitor	Cilazapril	3
	Perindopril	1
	Ramipril	8
Diuretic	Furosemide	1
	Hydrochlorothiazide	4
	Indapamide	6
	Torasemide	1
Beta-blocker	Bisoprolol	2
	Metoprolol	1
Calcium channel blocker	Amlodipine	5
Proton Pump Inhibitor	Pantoprazole	3
Statin	Simvastatin	2
Opioid pain medication	Tramadol	1
Other analgesics	Paracetamol	1
Angiotensin II receptor antagonist	Losartan	1
Antihyperglycemic Agent	Metformin	1

Supplementary material - Identified Triple Whammy – summary.							
	Age		International name	Formulation	Dose	Dosage	Package(d)
1	91	1	Torasemide	tablets	10mg	1x1	1
		2	Omperazole	capsules	20mg	1x1	1
		3	Metoprolol	tablets	50mg	2x1	1
		4	Meloxicam	tablets	15mg	1x1	2
		5	Ramipril	tablets	5mg	2x1	4
2	71	1	Amlodipine	tablets	5mg	1x1	1
		2	Ramipril	tablets	5mg	1x1	1
		3	Ketoprofen	tablets	150mg	1x1	1
		4	Indapamide	tablets	1,5mg	1x1	1
3	56	1	Diclofenac	controlled-release tablet	150mg	1x1	1
		2	Hydrochlorothiazide	tablets	12,5mg	1x1	2
		3	Cilazapril	coated tablet	5mg	1x1	1
		4	Pantoprazole	enteric-coated tablet	20mg	1x1	1
4	57	1	Bisoprolol	coated tablet	5mg	1x1	1
		2	Losartan + Hydrochlorothiazide	coated tablet	100mg + 25mg	1x1	1
		3	Ramipril	tablets	5mg	1x1	1
		4	Metformin	coated tablet	1000mg	3x1	1
		5	Diclofenac	coated tablet	100mg	2x1	1
5	71	1	Amlodypine	tablets	5mg	1x1	1
		2	Ramipril	tablets	5mg	1x1	1
		3	Ketoprofen	tablets	150mg	1x1	1
		4	Indapamide	tablets	1,5mg	1x1	1
6	71	1	Amlodipine	tablets	5mg	1x1	1
		2	Ramipril	tablets	5mg	1x1	1
		3	Ketoprofen	tablets	150mg	1x1	1
		4	Indapamide	tablets	1,5mg	1x1	1
		5	Simvastatin	coated tablets	20mg	1x1	1
7	71	1	Amlodipine	tablets	5mg	1x1	1
		2	Ramipril	tablets	5mg	1x1	1
		3	Ketoprofen	tablets	150mg	1x1	1
		4	Indapamide	tablets	1,5mg	1x1	1
		5	Simvastatin	coated tablets	20mg	1x1	1
8	90	1	Furosemide	tablets	40mg	1x1	1
		2	Bisoprolol	Coated tablets	10mg	1x1	1
		3	Ramipril	tablets	10mg	1x1	1
		4	Diclofenac	controlled-release capsules	75mg	2x1	1
9	56	1	Pantoprazole	enteric tablets	20mg	1x1	1
		2	Hydrochlorothiazide	tablets	12,5mg	1x1	1
		3	Diclofenac	controlled-release tablets	150mg	1x1	1
		4	Cilazapril	coated tablets	5mg	1x1	1
10	71	1	Amlodipine	tablets	5mg	1x1	1
		2	Ramipril	tablets	5mg	1x1	1
		3	Ketoprofen	tablets	150mg	1x1	1
		4	Indapamide	tablets	1,5mg	1x1	1
11	58	1	Perindopril + Amlodipine	coated tablets	5mg	1x1	1
		2	Indapamide	controlled-release tablets	1,5mg	1x1	1
		3	Paracetamol + Tramadol	coated tablets	375mg + 325mg	2x1	1
		4	Diclofenac	controlled-release tablets	75mg	1x1	1
12	56	1	Pantoprazole	enteric tablets	20mg	1x1	1
		2	Hydrochlorothiazide	Tablets	12,5mg	1x1	1
		3	Diclofenac	controlled-release tablets	150mg	1x1	1
		4	Cilazapril	coated tablets	5mg	1x1	1

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