Primary Non-adherence to Pharmacotherapy Among Patients With Chronic Diseases: A Case Study of Slovakia

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Research Article

Keywords: ePrescription, adherence, pharmacotherapy, hypertension, diabetes mellitus, hypercholesterolemia

Posted Date: August 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-716374/v1>

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Abstract

Background

ePrescription enables to investigate primary non-adherence (PNA) to pharmacotherapy by studying the percentage of prescriptions which have been issued (a prescription record present) but not dispensed in a pharmacy (a dispensation record missing) out of a total number of registered prescriptions. Identification of non-adherence enables to analyze its causes and target them efficiently.

Methods

This paper investigates PNA rate for prescriptions issued to patients with chronic diseases such as hypertension, diabetes mellitus and hypercholesterolemia (N=108 735), and its dependence on the following variables: geographic location, age, sex, social status, physicians specialty and the level of patient's co-payment for medications. The presented dataset comprises a private health insurance company's prescription data collected over a period of 12 months (January 2018 – December 2018).

Results

The PNA rate for ePrescriptions issued to patients with the above-mentioned chronic diseases reached up to 4.0%. In general, the PNA rate showed decrease with increasing comorbidity as well as with age. Primary non-adherence rates were lowest for the prescriptions written by general practitioners (3.6%). Among health insurance premium defaulters who pay the full price of prescribed medications, the PNA rate showed decrease with their cost. Significantly higher PNA rate was observed among premium payers (40.4%) compared with premium defaulters (3.5%).

Conclusions

Interestingly, the very high rate of adherence among patients with chronic diseases exceeds the numbers previously reported in the literature, where adherence rate $\geq 80\%$ is described as 'good' adherence. This could be partially explained by the fact that the present study included only chronic-disease patients undergoing a medical treatment – non-diagnosed patients or patients without a medical treatment were not considered.

Background

According to the World Health Organization (WHO), adherence to long-term therapies for chronic diseases averages 50% in developed countries [1]. Concurrently, adherence to medication significantly reduces the risk of complications [2]. On the other hand, non-adherence increases the healthcare costs for chronic diseases. Furthermore, the cost savings due to the lower total costs for pharmacotherapy are then exceeded by additional costs as a consequence of treating the complications (which stem from neglecting the chronic disease treatment) [3], [4].

Primary non-adherence (PNA) is defined as the failure to fill a prescription. Thence, comparing physicians' prescription records and pharmacy dispensation records enables to identify the rate of primary non-adherence to prescribed medications with respect to the type of patients, physicians, their specialty, diagnosis, medications, their cost and co-payments as well as geographic location. Early detection of PNA can result in targeted communication with patients as well as can help to identify its causes and address them [5].

MEMS (*Medication event monitoring system*) [6] is considered to be the gold standard in monitoring medication adherence. MEMS are devices which monitor the time each time a medication bottle is opened. The prospective study in Spain [7] showed that dispensation of ePrescriptions is a valuable tool to identify pharmacotherapy adherence in hypertension. In this study, the authors compared adherence to ePrescription with adherence measured by MEMS after 6, 12, 18 and 24 months, and they found no significant differences between the results obtained by the two approaches.

Based on the ePrescription data analysis in Poland the overall PNA rate [8] reached 20.8%, corresponding to 94 913 filled ePrescriptions out of a total of 119 880. The PNA was found to decrease with age, the lowest PNA was in the age group 75+ years. In Poland, patients in this age group are entitled to obtain selected medications free of charge. The PNA rate for the medications involved in this scheme was lower by 3 percentage points.

In Hungary [5], the PNA to medications prescribed by general practitioners for the time period 2012–2015 was 35.9%. The PNA was lower in the age group 65+ years than in the group 45–64 years (37.9%). Patients from vulnerable groups who are eligible for lower co-payments had lower PNA rate (21.7%). Higher PNA rate was associated with urban settlements, higher level of education as well as vacancy of the general practices.

Meta-analysis [9] of seven studies with a total number of patients 200 000 revealed 11% higher PNA rate in the groups of patients who are subject to co-payments for medications compared with the ones without co-payments.

The aim of the present study is to determine the PNA rate for prescriptions issued to patients with hypertension, diabetes mellitus and hypercholesterolemia in Slovakia as a dependence on their geographic location, age, sex, social status, physician specialty and the level of patient's co-payment for medications.

Health system and pharmaceutical policy in Slovakia

In Slovakia, health insurance is mandatory: economically active policyholders are obliged to pay contributions to the public health insurance, while the state pays contributions for economically inactive population (children, unemployed, people living below the poverty line, people on maternity/paternity leave, pensioners). Policyholders are entitled to get categorized medications reimbursed; their price, the level of reimbursement and thence the level of co-payment is determined by a regulator. Premium

defaulters (defined as those that did not pay their health insurance premium) are eligible only for acute and emergency healthcare until they set up a payment schedule with their health insurance company. Maximum limits for co-payments are set by law for children, severely disabled and pensioners – if the total sum of co-payments per quarter exceeds the set limit, the health insurance company reimburses the patient the amount overpaid. The maximum limits for co-payment vary between different groups of people, the limit is set at 30 €/quarter for pensioners, 12 €/quarter for severely disabled people. It is the sum of co-payments for the cheapest generic alternatives of prescribed medications which is taken into account when assessing whether the maximum limit for co-payment was reached.

Methodology

The dataset comprises Dôvera health insurance company's records of healthcare provided to their policyholders (1 478 854 policyholders on 01st January 2018, 28.7% share of the public health insurance market in Slovakia). Here we studied the ratio of pharmacy dispensation records to physicians' prescription records on the sample of 108 735 patients with the chronic diseases hypertension, diabetes mellitus and hypercholesterolemia in relation to the pharmacotherapy of these diseases. This ratio can be used to determine the PNA rate as follows:

$$PNA = \left(1 - \left(\frac{\sum \text{dispensationrecords}}{\sum \text{prescriptionrecords}} \right) \right) \times 100[\%]$$

When PNA was examined by physician specialty, only the physicians who provided medical treatment to a minimum of 10 patients were considered in the analysis. The relation between the PNA and the extent of co-payment for medications was assessed for health insurance premium payers (are subject only to the co-payment for medications) and defaulters (are subject to the full cost of medications) separately.

Classification of chronic-disease patients during the classification period (according to the use of medications in the one-year period 1/2017–12/2017 or else according to the diagnoses reported in the two-year period 1/2016–12/2017).

Patient with hypertension (N = 256 838) was prescribed and had their prescriptions for at least 121 standard drug doses of antihypertensive drugs (from Anatomical Therapeutic Chemical (ATC) class C02, C03, C07, C08, C09) filled during the one-year classification period or else had during the two-year classification period at least two records of doctor's appointments with the diagnosis of hypertension (110–113 based on Classification of Diseases ICD – 10).

Patient with type 1 or type 2 diabetes mellitus (N = 70 143) was prescribed and had their prescription for at least 1 standard drug dose of antidiabetic drugs (from ATC class A10A and A10B) filled during the one-year classification period or else had during the two-year classification period at least two records of doctor's appointments with the diagnosis of diabetes mellitus (E10, E11 based on ICD-10).

Patient with hypercholesterolemia (N = 129 804) was prescribed and had their prescriptions for at least 121 standard drug doses of hypolipidemic drugs (from ATC class C10) filled during the one-year

classification period or else had during the two-year classification period at least two records of doctor's appointments with the diagnosis of hypercholesterolemia (E78 based on ICD-10).

Patients could have multiple chronic diagnoses at the same time. According to the above-mentioned classification the total number of patients with hypertension, diabetes mellitus and/or hypercholesterolemia during the reference period was 310 325.

2. ePrescription during the reference period

In this study we analyzed ePrescription records from a 12-month period (1/2018–12/2018) with dispensation by 01/2019 among patients with the above-mentioned chronic diseases who during the reference period did not have any paper prescription for medications to treat these diseases filled in a pharmacy (they could be given paper prescriptions for medications to treat other diseases). In patients who were prescribed medications exclusively through ePrescription, there is a higher probability that their prescribing physicians fully use ePrescriptions. The presence of paper prescriptions which match dispensation records of a patient who is treated for the above-mentioned diseases increases the risk that they got more of such prescriptions; however if they did not have these prescriptions filled in a pharmacy they were not included in the PNA analysis. During the reference period **108 735** patients were given exclusively ePrescriptions for medications to treat hypertension, diabetes mellitus and/or hypercholesterolemia. Out of these 91 386 suffered from hypertension, 17 607 from diabetes mellitus and 40 643 from hypercholesterolemia; the patients could suffer from more than one of these diseases.

To compare these results with average PNA, we calculated the PNA rate taking into account all ePrescriptions for all medicines prescribed to all patients during the reference period.

The patients were divided into groups according to age, social status, the level of co-payment for medications and their price, health insurance premium payment, chronic disease they suffer from (hypertension, diabetes mellitus and/or hypercholesterolemia), the type of medications they take and the geographic location where they live. We investigated patients' tendency to fill their prescriptions in a pharmacy based on the specialty of the physician who prescribed them. Within these categories we investigated statistically significant differences in individual groups using the following tests: the Spearman's correlation coefficient, the Pearson's Chi-squared test, the Fisher's exact test, the Kolmogorov-Smirnov test (Table 1).

Results

Patients with hypertension, diabetes mellitus and/or hypercholesterolemia who were given exclusively ePrescriptions for medicines to treat these diseases (N = 108 735) were during the reference period prescribed 926 062 ePrescriptions; out of which 889,204 (96.02%) were filled in pharmacies, i.e. the PNA rate was 3.98% (men: 4.09%, women 3.87%; N = 52 353 and 56 382, respectively). 88 789 (81.66%) patients had all their prescriptions filled, i.e. their PNA rate equaled 0%.

Category	Type of test	Result	Note
Age	Spearman' correlation coefficient	The correlation between age and PNA is statistically significant. rho= -0.05867221 p-value < 0.001	We considered the fact that we have a sufficiently large sample and that the sample Spearman's correlation coefficient asymptotically approaches the normal distribution. Test statistics u = -14.85439
Social status	Fisher's exact test	Patients' social status significantly affects their PNA rate. p-value < 0.001	For all categorical variables we used the Pearson's Chi-squared or the Fisher's exact test (in case the frequency was lower than 5 in any of the categories).
Health insurance premium payment	Kolmogorov-Smirnov Test	The groups of premium payers and defaulters have different PNA rates. p-value < 0.001 Defaulters have higher PNA rate.	We chose the K-S test because the distribution functions of the variables differ in shape and variance.
Co-payments	Pearson's Chi-squared test	The level of co-payment for payers statistically significantly affects their PNA. p-value = 0.001543	Linear regression on the group means (p = 0.00629) and the significance test of the Spearman's correlation coefficient (p = 0.0008261) were also used.
Medication cost	Fisher's exact test	The level of co-payment for defaulters statistically significantly affects their PNA. p-value < 0.001	Linear regression on the group means (p = 0.117) and the significance test of the Spearman's correlation coefficient (p = 2.029e-13) were also used.
Chronic diseases	<i>Pearson's Chi-squared test</i>	The co-existence of chronic diseases in patients statistically significantly affects their PNA. p-value < 0.001	

Note: The significance level = 0.05

Category	Type of test	Result	Note
Type of medication	<i>Pearson's Chi-squared test</i>	PNA is dependent on the type of medication prescribed on a prescription. p-value < 0.001	
Physician specialty	Fisher's exact test	PNA differs depending on the specialty of prescribing physicians. p-value < 0.001	
Region	<i>Pearson's Chi-squared test</i>	The geographic location of a patient significantly affects the PNA rate. p-value < 0.001	
Note: The significance level = 0.05			

Table 1 Statistical analysis of the influence of selected factors on PNA,

Age

The PNA to ePrescription showed decrease with patient's age, from 10.0% in the age group 19–25 years to 2.5% in the age group 76 + years (Fig. 1).

Social status: The PNA rate for prescriptions issued to pensioners (3.16%; 95% CI: 3.11–3.20%; N = 58 481) was lower than among employees (4.26%; 95% CI: 4.13–4.34%; N = 36 742) or self-employed people (5.51%; 95% CI: 5.28–5.74%; N = 5 448). Among unemployed people the PNA rate reached 9.19% (95% CI: 8.84–9.55%; N = 3 240) while among those whose income falls below the poverty line 14.20% (95% CI: 13.34–15.07%; N = 807).

Health insurance premium payment: By law [10] policyholders who default on their health insurance premium payments are not entitled for other than acute and emergency healthcare, and they have to pay the full cost of the medications prescribed to treat chronic diseases. The PNA to ePrescriptions issued to defaulters was 40.44% (95% CI: 39.53–41.35%; N = 1 767), see Fig. 2.

Co-payments: Among health insurance premium payers, the PNA rate for the medications which are fully covered by health insurance was 3.71% (95% CI: 3.61–3.80%; n = 145 975 prescriptions), while the PNA rate for the medications which are subject to co-payments was on average 3.50% (95% CI: 3.46–3.55%; n = 768 962 prescriptions). The average PNA rate in the co-payment categories up to €15 per prescription was lower than 4%. Substantial increase in the PNA rate was observed for the medications which are

subject to co-payments higher than €30. These were, however, represented by a small sample size (Fig. 2).

Medication cost

Among health insurance premium defaulters, the PNA rate showed decrease with increasing cost of medication, i.e. prescriptions for more expensive medications were filled more often (Fig. 3).

Combination of chronic diseases: The PNA rate showed decrease with increasing comorbidity. The lowest PNA rate among patients with a single chronic disease was in patients suffering from hypertension (4.35%; 95% CI: 4.29–4.41%; N = 59 110), followed by patients with hypercholesterolemia (5.03%; 95% CI: 4.78–5.27%; N = 9 907) and patients with diabetes mellitus (5.83%; 95% CI: 5.57–6.09%; N = 3 895), respectively. The PNA rate in patients suffering from all three above-mentioned chronic diseases was 3.33% (95% CI: 3.23–3.44%; N = 5 528).

Type of medication: The lowest PNA rate was observed for hypertension medications (3.73%; 95% CI: 3.69–3.78%; n = 692 527 prescriptions). The PNA rate for insulin medications was 3.9% (95% CI: 3.62–4.16%; n = 19 388 prescriptions), for hypolipidemic drugs 4.61% (95% CI: 4.49–4.73%; n = 118 297 prescriptions), for peroral antidiabetic drugs 4.95% (95% CI: 4.78–5.12%; n = 64 806 prescriptions) and for medical aids for diabetics 5.08% (95% CI: 4.84–5.33%; n = 31 044 prescriptions).

Physician specialty: The lowest PNA rate (3.62%; 95% CI: 3.58–3.67%) was observed for ePrescriptions written by general practitioners (n = 718 723 prescriptions), followed by internists (PNA 5.09%; 95% CI: 4.92–5.25%; n = 67 533 prescriptions), diabetologists (PNA 5.12%; 95% CI: 4.99–5.25%; n = 107 258 prescriptions) and cardiologists (PNA 5.51%; 95% CI: 5.24–5.78%; n = 27 299 prescriptions). (**Appendix 1**).

Region

The PNA to ePrescription was lowest in the Trenčín and Prešov regions (**Appendix 2**).

All of the Dôvera health insurance company policyholders were in 2018 given 12 603 133 ePrescriptions, out of which 9 484 689 were filled in pharmacies (75.26%), which gives the overall PNA rate of 24.74% (95% CI: 24.72–24.77%).

Discussion

To the best of our knowledge, the PNA rate among chronic-disease patients in the present study is lower than previously reported in the literature, where $\geq 80\%$ is described as 'good' adherence (i.e. PNA rate $\leq 20\%$) [11]. This can be partially explained by the methodology applied in this study. In the administrative data of health insurance companies diseases can be identified based on healthcare provision records: a chronic-disease patient can be thus identified based on healthcare provided within a certain time frame. It should be noted that only chronic-disease patients undergoing medical treatment were included in the analysis; patients who were not diagnosed or did not undergo medical treatment were not considered. In

this study we analyzed only dispensation of issued prescriptions irrespective of whether the medication dosing was adequate throughout the reference period. In case a patient skipped a doctor's appointment and as a result of that was not given another prescription, the PNA rate was not affected.

The observed decrease in the PNA rate with age agrees well with the previous studies, e.g. from Poland[8] or Hungary [5]. The policyholder's social status category tends to correlate with their age, which is reflected in the PNA rates. Pensioners tend to have lower PNA rate which might be linked to the scheme according to which they are eligible for getting part of their co-payments for medications reimbursed. Patients from socially disadvantaged groups (unemployed, with income below the poverty line), premium defaulters (private payers and self-employed) had high PNA rates. It is debatable, especially in the group of defaulters, whether it is economically efficient to deny them access to chronic disease treatment while covering the treatment of their acute complications which stem from neglecting the treatment of their chronic disease.

The dependence of the PNA rate on the level of medication co-payment/cost showed contradictory results compared with the majority of previous studies ([12]; [9]; [13]). In the case of defaulters who are subject to the full cost of medication we observed decrease in the PNA rate with increasing medication cost, which is opposite behavior than expected based on the economic theory. It should be noted though that here the sample size was relatively small (1 767 patients, 11 125 prescriptions). A possible explanation could be higher price of some of the essential medications (e.g. insulin) where demand flexibility is limited; the extent of healthcare need becomes a more important determinant of adherence than the level of co-payment.

Among health insurance premium payers, the PNA rate for medications with co-payments lower than €15 was at its lowest and without fluctuations. Substantial increase in the PNA was observed only for the medications with co-payments higher than €30, where, however, the sample size was rather small. Surprisingly, prescriptions for the medications without co-payments were linked with higher PNA than for the ones with non-zero co-payments. When trying to find an explanation for the inverse relation between the PNA rate and patients' financial burden we can not neglect the effect of perceived value on behavioral intention. "More expensive" is perceived as "better", "more effective" [14], and may increase the motivation of patients to have their prescription filled in a pharmacy.

Despite the differences in the average PNA rate between the four types of most prescribing specialties are not large, the PNA distribution among individual physicians confirms that the ePrescriptions written by general practitioners achieve the best dispensation rate; only 5.6% of all general practitioners has PNA rate higher than 10%, while it is 16.5% in the case of diabetologists. These differences should be analyzed in more detail as they indicate possibility of potential improvement of patient adherence by extending prescribing competences of general practitioners with lower PNA rate. Equally, regional differences, which distinguished two regions in Slovakia from the rest of the country, should be investigated in more detail too.

Conclusions

In summary, the present study has shown that compared with the average PNA of all electronic prescription records in Slovakia, ePrescription among patients with chronic diseases is accompanied with a very low rate of PNA, which is inevitable for successful pharmacotherapy. The PNA was shown to decrease with age as well as with increasing comorbidity. Co-payments up to €15 for chronic disease medications do not hamper access to pharmacotherapy. The prescriptions written by general practitioners showed the lowest PNA rate. Further analysis of the presented dataset will be needed for developing interventions aimed at improving patient adherence to medical treatments.

Abbreviations

PNA: Primary Non-Adherence

WHO: World Health Organization

MEMS: Medication Event Monitoring System

ATC: Anatomical Therapeutic Chemical

ICD: Classification of Diseases

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to §76 of Act no. 581/2004 Coll., on Health Insurance Companies and Health Care Surveillance, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

TS wrote the manuscript and researched data. PI a TS designed the study concept and contributed to the analyses. RM reviewed and edited the manuscript and contributed to the discussion. VK a BB contributed to the analysis and discussion. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

Note: N denotes the number of patients

Figure 1

PNA as a function of patients' age.

Note: n denotes the number of prescriptions

Figure 2

a) PNA as a function of health insurance premium payment and b) PNA among premium payers as a function of the level of co-payments.

Note: n denotes the number of prescriptions

Figure 3

PNA among premium defaulters as a function of medication cost.

Supplementary Files

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