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Determinants of Primary Nonadherence to Prescribed Medications among Adults in Hungary

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1 Introduction

Adherence to prescribed medications refers to taking medications as described or prescribed by health care providers. It is used to reflect the degree to which patients follow instructions and recommendations of health care providers throughout the prescribed treatment course. The adherence process entails three main elements: initiation of therapy; implementation of the therapy as prescribed; and persistence on the given therapy for the desired period of time.

Nonadherence has become an important public health issue in the recent years. This concern is due to its' role in mediating therapeutic outcomes of the prescribed medications. Adherence is considered as the cornerstone in management, control, and prevention of loss of the desired therapeutic outcome, disease progression, and complications. Several pieces of research attributed higher morbidity and mortality among patients with chronic diseases, premature disability, adverse outcomes, health disparities, and reduced work and productivity, increase health care cost, hospitalization, and deterioration of quality of life to medication noncompliance.

The WHO classified the factors that affect medication adherence into five main categories. Patients' demographic and socioeconomic factors such as age, sex, and education. Factors related to the patient including cognitive ability, expectations and forgetfulness. Factors related to the medical conditions of the patient such as comorbidity and poly-pharmacy. Factors linked to the health care system like drug price, insurance, team work, organization and patient-physician relationship. Treatment-related issues such as side effects and complexity of the prescribed regimens.

Nonadherence is prevalent across the globe. A meta-analysis of 20 studies conducted between 1998 and 2010 in Australia, Canada, USA, and Europe indicated that around 50% of patients did not properly adhere to cardiovascular medications prescribed for preventive purposes. A systematic review and meta-analysis of several studies indicated that about one-third of the written prescriptions are not

dispensed and around 50% of the dispensed medications are not taken as recommended.

Several interventions were tried to enhance adherence. Some interventions tested globally included simple dose adjustment, reducing number of the medications, and educational interventions. Other interventions included more complex strategies such as expansion of the pharmacist role in health care, enhancing patient-physician communication, provision of services, and proper description of disease and medications.

Evidence from the "European Social Survey" indicated that nonadherence rate to prescribed medications in Hungary was 20.3%, giving it the 4th highest rate of nonadherence among the 24 European countries surveyed. This probably indicates importance of nonadherence as a contributing factor to high amenable mortality in the Hungarian context, which is more than twice the average in the European Union based on the EUROSTAT statistics of 2015.

The Swiss Hungarian Cooperation Programme (SHCP) entitled "Public Health Focused Model Programme for Organizing Primary Care Services Backed by a Virtual Care Service Centre" was implemented as a pilot project in the disadvantaged and the most disadvantaged areas of the country. The programme entailed establishing general practice clusters (GPCs) for expansion and strengthening of the PHC role to include health promotion activities to improve health determinants and equity among the disadvantaged and the most disadvantaged groups, disease prevention, health restoration, and rehabilitation activities in a well-organized and collaborated manner.

The health status of the Hungarian population is inferior to that of the majority of the European countries. Given that adherence is essential for achieving desired clinical outcomes, reducing morbidity and mortality, prevention of disease progression and complications, reducing health care costs, and improving the overall quality of life, studying nonadherence and uncovering its major determinants is essential. Indeed, primary nonadherence has not been investigated previously in

Hungary at the national level. Thus, studying and understanding nonadherence in Hungary are indispensable.

2 Objectives

The aims of our investigations were to:

(1) Estimate primary nonadherence to prescribed medications written in the general medical practices (GMPs) among adults in Hungary using the WHO key indicator of patient care "percentage of drugs actually dispensed" to quantify the dispensed medications at the period between 2012 and 2015, and to describe variation of adherence across GMPs.

(2) To determine effects of GMP structure and patient characteristics on adherence.

(3) To evaluate whether operating the GPC model for the purpose of organizing and improving effectiveness of PHC increases percentage of drugs actually dispensed reflecting eventually better patient-physician collaboration.

3 Methods

3.1 Setting

In this study, we performed secondary data analyses. Analysis unit was the prescription written by a GP working in PHC and filled by patient. Data on prescribed and dispensed prescriptions were obtained from the National Health Insurance Fund (NHIF). The data investigated covered all GMPs running in Hungary for the period between January 2012 and September 2015.

As far as the SHCP is concerned, Hungarian PHC teams working in GMPs (each GMP team consists of one GP and one practice nurse) were invited to establish the GPCs in 2012. The aim of this community-oriented approach was to reorient the PHC system in Hungary in order to improve the general health status and quality of life of the population.

Four GPCs were established in four districts of Hungary. Each cluster consisted of six GMPs. The GPC was created with the aim of offering preventive services and health promotion interventions besides the usually given acute, curative, and emergency services. The work of the GPC was supported by other health professionals such as one community nurse, one dietician, one psychologist, one physiotherapist, two specialists in public health, and twelve health mediators.

In 2014, the new health care services were initiated. An invitation was given to all adults aged 18 years and above whose GMPs participated in the programme to take part in an organized assessment of health status carried out by the community nurse and the public health specialists.

Three new activities –which were not available before- were introduced into primary health care system: assessment of health status at the beginning and at the end of the programme to detect differences in health conditions; medical risk assessment to estimate significance of risks factors or morbidities evaluated during health status assessment carried out by a GP; and then the GP refers patients to treatment or lifestyle counseling to be offered by dieticians, physiotherapists, psychologists, or public health specialists to manage risk factors, foster

health literacy, and motivate patients to adhere to medications and advice of health professionals. In addition, a new dimension towards rehabilitation was introduced into chronic care services to assist disabled to achieve social integration through proper collaboration between physicians and other health care providers.

3.2 Data collection

During medical practice, the NHIF data that cover the whole country were aggregated into four quarters per annum and stratified by the patient's sex, age (5-year bands), and holding an exemption certificate. The prescribed drugs were classified based on the Anatomical Therapeutic Chemical (ATC) Classification proposed by the WHO into 14 groups. The data analyses did not encompass antineoplastic and immunomodulating agents, antiparasitic drugs, insecticides and repellents since prescribing those medications were not linked to GMPs as per the Hungarian regulations.

Characteristics of the GMPs were also obtained from the NHIF. The characteristics included information on vacancy of the GMP as to whether the health care service is provided by a temporary contracted GP available at a specific time and place or a permanent GP available persistently. The GMPs were also classified as being in an urban or rural setting. Size of the locality based on the number of adults to which health care services were provided based on the categorization of the NHIF (less than 800, 801–1200, 1201–1600, 1601–2000, and 2001 or more clients) was included. In addition, geographical location by the county where the GMPs were operating was investigated. Furthermore, the socioeconomic status of clients receiving health care services in a GMP was reflected by their internally standardized relative education estimated by the indirect standardization method. This was completed using gender and age group-specific levels of education of the Hungarian Census of 2011 and the gender and age group structure of the related GMP clients. The national socio-economic status average equals value 1 of the internally standardized relative education.

3.3 Statistical analysis

Outcomes measured (dependent variables)

The outcomes measured were the primary adherence ratios indirectly standardized for sex, age, and possession of exemption certificates. The standardized adherence ratios were obtained by dividing the accumulated GMP-specific numbers of the observed (O) dispensed medications (prescriptions) by the accumulated GMP-specific numbers of the expected (E) dispensed medications (prescriptions).

The NHIF determined age-, sex-, and exemption certificate-specific number of both the written and the dispensed prescriptions and proportion of drugs actually dispensed (dispensed to written ratio, DWR) as an indicator of primary adherence for each ATC group of drugs studied during the entire period of investigation for the whole country.

The expected number of dispensed prescriptions was estimated for each GMP using the age-, sex-, and exemption certificate-specific number of the written prescriptions and the national reference DWRs (summing up the expected number of medications dispensed in all strata). The ratio of the registered number of dispensed prescriptions in a GMP and the estimated GMP-specific expected number of dispensed prescriptions was calculated to indicate GMP-specific standardized dispensed to written ratios (SDWRs) for each ATC group studied.

SDWR values obtained were tested for normal distribution. Results of the Kolmogorov-Smirnov test showed that these data were not normally distributed. To describe their distribution, median values and interquartile ranges were used.

Generalized linear regression modeling

In order to identify the major determinants of the SDWRs while controlling for the time, generalized linear regression modeling was performed. We calculated generalized linear regression coefficients (b) along with their corresponding 95% confidence intervals (95%CI). Both

vacancy of GMP and type of settlement were inserted into the model as binary parameters. However, county location and size of the GMP were inserted into the model as dummy variables with Budapest as a reference category for county location and size of the GMP serving 1601-2000 clients as a reference category for GMP size. Pearson chi-square goodness of fit was used to indicate regression modeling performance. The significance level was set at 95% ($p<0.05$). SPSS version 20 was used to analyze the data.

3.4 Evaluation of the SHCP

The effectiveness of the intervention has been evaluated by before-after analyses of the programme. We aggregated data on the number of prescriptions written by the GPs and dispensed by the clients and calculated the DWRs in the first quarter of 2012 (2012Q1, before the intervention) and in the third quarter of 2015 (2015Q3, after the intervention) for both the intervention area and the whole country.

The DWRs for the aggregated intervention population were calculated by age, sex, and exemption certificate eligibility and compared with the DWRs of the whole country before and after the intervention programme. In addition, SDWRs for each ATC group was calculated and compared. Relative dispensing ratios (RRs) for 2015Q3 and 2012Q1 were calculated for each ATC group using 95% CI of the measures to indicate the impact of the programme on the DWRs.

3.5 Ethical considerations

This research involved secondary data analyses. It did not reflect any personal information or identifier. In line with the Hungarian rules and regulations, no ethical approval is required to carry out this type of study analysis.

4 Results

4.1 Prevalence of primary nonadherence among adults in Hungary

Characteristics of the GMPs running across Hungary

Overall, 4856 GMPs were running around the country. 3.3% of the GMPs were vacant, two-third were located in urban areas. The majority of the GMPs were running in localities serving more than 1200 clients. 18% of the GMPs were running in Budapest County which is used as a reference category in our analysis, 5.1% were in Hajdú-Bihar, 4.0% were in Fejér, and 2.9% were operating in Zala County. The mean relative education of clients was 1.00 (SD±0.10) using the internally standardized approach.

Proportion of drugs actually dispensed by patient characteristics for total practice

The percentage of prescriptions dispensed for the entire practice was 64.1%. The DWR showed significant variation across age groups with better adherence of 65.8% reported for elderly adults aged 65 years and above. By gender, slight differences were reported with 64.5% for females and 63.6% for males. Adults holding exemption certificates reported the highest DWR of 78.3%. Indeed, variation in the distribution of the adherence by sex and exemption certificate has been detected in each ATC group investigated. However, variation by age groups differed by the ATC group.

Proportion of drugs actually dispensed by ATC groups

A wide variation of DWRs by drug class was reported. The lowest DWR among ATC groups was reported for agents used for the cardiovascular system at 59.4%. The highest DWR was detected for anti-infective drugs for systemic use with 79.1%.

Distribution of dispensed to written ratios of prescribed medications by ATC groups

Since data were not normally distributed, median and interquartile ranges were used in the description. Median was 1.09 for alimentary tract and metabolism drugs, blood and blood-forming agents, and cardiovascular system drugs with corresponding interquartile range 34%, 36%, and 42%, respectively. Median was 1.04 for anti-infective drugs for systemic use and the interquartile range was 14%.

4.2 Predictors of nonadherence among adults for the total practice in Hungary

The results of the generalized linear regression model showed that there was an inverse association between SDWRs and relative education of patients [b=-0.440, 95%CI: -0.468;-0.413], vacancy of the GMP [b= -0.193, 95%CI: -0.204;-0.182], and living in urban areas [b= -0.099, 95%CI: -0.103;-0.094]. A better SDWRs was noted for GMPs running in a relatively smaller localities [$b_{X\text{-}800}$= 0.052, 95%CI: 0.041; 0.063, $b_{801\text{-}1200}$= 0.031, 95%CI: 0.025; 0.037, $b_{1201\text{-}1600}$= 0.017, 95%CI: 0.013; 0.022] compared to those running in larger localities [$b_{2001\text{-}X}$= -0.014, 95%CI: -0.019;-0.009]. The geographical location of the county was an important determinant. The generalized linear regression coefficient showed that living in urban areas, vacancy of the GMP and higher levels of education of the clients were the major determinants associated with reduced levels of SDWRs. Komárom-Esztergom county and Somogy county reported a positive association with SDWRs for the entire period studied while Fejér county reported significant negative association for the same period.

4.3 Evaluation of the SHCP

Dispensed to written ratios by patient sociodemographic characteristics in Hungary

In 2012Q1, the overall DWRs were 69.3%. However, in 2015Q3 DWR was reduced to 60.8%. No significant differences were noted between

males and females before and after the intervention. Across age groups, elderly adults 65 years and above reported better adherence in both periods [71.2% in 2012Q1 and 62.4% in 2015Q3] while middle-aged adults reported the lowest rate [67.2% in 2012Q1 and 58.6% in 2015Q3]. Adherence was significantly higher among patients holding exemption certificate [80.1% in 2012Q1 and 75.8% in 2015Q3] compared to those without exemption certificate [67.9% in 2012Q1 and 59.2% in 2015Q3]. Reduction in DWRs was detected in every socioeconomic stratum and was shown to be significant when checked by the chi-square test ($p<0.001$).

Dispensed to written ratios by ATC group of drugs in Hungary

The highest DWRs were reported for anti-infective drugs for systemic use (ATC J) [80.1% in 2012Q1 and 76.1% in 2015Q3]. The lowest DWRs were reported for various drug groups (ATC V) [57.6% in 2012Q1] and for cardiovascular system agents (ATC C) [55.3% in 2015Q3]. Overall, there was a statistically significant reduction in DWRs in every ATC group over time (excluding the ATC V group of drugs) as indicated by the chi-square test ($p<0.001$).

Dispensed to written ratios by patient sociodemographic characteristics in the intervention area

In 2012Q1, the number of prescriptions written was 134,470 and the number of dispensed prescriptions was 98,213. The observed DWR was 73.0%. Slight differences were observed by gender and age on adherence. The significant difference was observed between clients with exemption certificates and those without exemption certificates. In 2015Q3, after the intervention, The DWR was reduced to 68.7% [133,689 prescriptions were written and 91,881prescriptions were dispensed]. The effects of sex and exemption certificates remained unchanged after the intervention. However, variation in DWR across age groups became very prominent [range was 72.2% - 73.9% before and became 66.5% - 70.8% after the intervention].

Dispensed to written ratios by ATC drug group in the intervention area

There was a significant variation across ATC drug groups. Before the intervention, the highest DWR was 81.8% reported for systemic hormonal preparations (ATC H) while the lowest was 61.2% and 68.8% reported for various drug group categories and cardiovascular system agents, respectively. After the intervention, systemic hormonal preparation remained the highest with 81.2% and cardiovascular agents reported the lowest DWR at 62.0%. ATC-specific DWRs wide variability remained unchanged.

Standardized dispensed to written ratios by ATC drug group in the intervention area

Variations in SDWRs by the ATC group were noted in the intervention area before and after the intervention and number of additionally dispensed prescriptions which was attributed to the intervention implemented. SDWRs indicated that overall adherence was generally higher in the intervention area than in Hungary for various ATC groups. SDWR for the entire practice was 1.042 in 2012Q1 and increased to 1.108 after the intervention in 2015Q3. When calculated the risk ratio (RR) for SDWRs, this change was shown to be significant [RR= 1.064; 95%CI: 1.054 - 1.073]. An excess number of prescriptions dispensed was 5033.2 in 2015Q3. The most significant impact observed was on both cardiovascular system drugs [RR= 1.062; 95%CI: 1.048-1.077] and alimentary tract and metabolism drugs [RR=1.072; 95%CI: 1.049-1.097] with 2143.5 and 1001.2 excess number of dispensed prescriptions in the intervention area, respectively. In addition, significant positive changes were observed for musculoskeletal drugs [RR=1.041; 95%CI: 1.010-1.074], blood and blood-forming organ drugs [RR=1.077; 95%CI: 1.044-1.111], and drugs of the nervous system [RR= 1.082; 95%CI: 1.047-1.118].

5 Study implications

High nonadherence to prescribed medications detected in this study contributes substantially to poor disease prognosis. Although this

dimension has not been investigated and estimated in our research, a low rate of adherence at 59.4% for cardiovascular system drugs the leading cause of death and the major determinant of life expectancy across European countries, the impact is expected to be great.

On the other hand, a high number of unfilled prescriptions result in considerable loss of time, work, capacities, and wastage of health care resources. Thus, the detected nonadherence can be assumed as an indicator of poor patient-physician cooperation.

In addition, evidence on the weak role of GPs in managing diseases of clients in urban areas and highly educated adult patients is observed. As a result, the monitoring system in PHC for primary medication adherence needs to be established to identify and manage the poorly performing GMPs.

Despite the fact that the SHCP did not entail specific activities to enhance adherence to medications, the programme confirmed that good patient-physician cooperation marked by massive care of patients through the extension of primary care activities to include preventive services improved adherence.

6 Conclusions and recommendations

About one-third of the prescribed prescriptions written by GPs working in PHC was not filled in Hungary indicating an overall alarming high rate of nonadherence. The study also demonstrated a wide variability of adherence across various GMPs. This variation can be attributed to GMP's structural characteristics, patients' socioeconomic status, and more importantly the magnitude and shape of patient-physician cooperation and communication style.

Regarding the SHCP, we found evidence that the extension of PHC services to include integrated and preventive services with proper protocol and necessary capacities enhanced medication adherence. This improvement was remarkable among adult patients with cardiovascular diseases and alimentary tract and metabolic disorders. The improvement of 6.4% reported in the programme without any specific activity for increasing adherence goes in line with published multifaceted intervention studies (range 4%-11%) devoted totally to enhance adherence.

In addition, our findings propose that DWRs can be used in routine monitoring of the operation of PHC and support substantial interventions. This finding endorses recommendations of the WHO in using the percentage of drugs actually dispensed in regular monitoring as a key indicator of patient care. Furthermore, measuring DWRs could be a useful indicator of the effectiveness of client- health care professionals' relationships in PHC.

7 New findings

Prevalence of primary nonadherence to prescribed medications in Hungary is high

More than one-third of the written prescriptions (35.9%) for the adult population in Hungary were not dispensed. Given that adherence is a key factor in achieving therapeutic goals and improving overall health status and quality of life, this high burden of nonadherence is crucial and suggested to be a major contributory factor to the poor health status and the high amenable mortality of the Hungarian population when compared to other Western European countries.

Prevalence of nonadherence varies by ATC group of drugs

The primary nonadherence differed by the ATC class of drugs. The best practice was reported for anti-infective drugs for systemic use (79.1% of the prescriptions were dispensed) while the worst practice was reported for medication used for the treatment of cardiovascular diseases (59.4% were dispensed). This is important not only in detecting differences in GMP's performance but also in identifying priorities where interventions are substantial.

Determinants of primary nonadherence among adults in Hungary are uncovered

We have detected and uncovered the major determinants of the high nonadherence to medications among adults. We found significant negative association between primary adherence and relative education of patients [b=-0.440, 95%CI: -0.468;-0.413], vacancy of the GMPs [b= -0.193, 95%CI: -0.204;-0.182], and living in urban areas [b= -0.099, 95%CI: -0.103;-0.094]. On the other hand, a better adherence was noted for GMPs running in a relatively smaller list sizes [$b_{X\text{-}800}$= 0.052, 95%CI: 0.041; 0.063, $b_{801\text{-}1200}$= 0.031, 95%CI: 0.025; 0.037, $b_{1201\text{-}1600}$= 0.017, 95%CI: 0.013; 0.022] compared to those running in larger list sizes [$b_{2001\text{-}X}$= -0.014, 95%CI: -0.019;-0.009].

Levels of adherence vary by the geographical location of the county

We have found variations in adherence ratios by the county's geography. Geographical location is an indicator of spatially important health-related variables like variation in the availability of health services and resources, certain lifestyle and culture, access to health care, and health literacy known well to impact adherence as documented in the literature. Thus, it could reflect health inequity across the country.

The SHCP improved the primary adherence in the intervention area

Extending PHC services to encompass preventive and rehabilitation services achieved significant improvement in adherence to prescribed medications. The magnitude of this improvement was 6.4% [RR= 1.064; 95%CI: 1.054 - 1.073] and corresponds to 5033.2 excess number of dispensed prescriptions. This improvement suggests that proper and intensive care of the clients improved their adherence without even conducting specific activities directing adherence itself.

Remarkable effects were noted on cardiovascular and alimentary tract and metabolism drugs

The major impact was noted on both cardiovascular system drugs [RR= 1.062; 95%CI: 1.048-1.077] and alimentary tract and metabolism drugs [RR=1.072; 95%CI: 1.049-1.097] with 42.6% and 19.9% an excess number of dispensed prescriptions achieved, respectively. This finding reflects that patients with diseases of high prevalence were more responsive to the intervention, and receiving more intensive health care services make patients more committed towards their regimens.

Percentage of drugs actually dispensed is a useful indicator of monitoring PHC

The indicator percentage of drugs actually dispensed can be used in routine monitoring of PHC operation and support the substantial interventions to improve overall health care services in PHC. This finding endorses recommendations of the WHO on the importance of the indicator in the health care process.

Percentage of drugs actually dispensed is a useful indicator of the patient-physician relationship

We noted that measuring dispensed to written ratios could be a useful indicator of the effectiveness of client- health care professionals' relationship and collaboration in PHC.

8 Funding

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9 Publications' list

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Candidate: Nouh Harsha
Neptun ID: C6NIJL
Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. **Harsha, N.**, Kőrösi, L., Pálinkás, A., Bíró, K., Boruzs, K., Ádány, R., Sándor, J., Czifra, Á.: Determinants of Primary Nonadherence to Medications Prescribed by General Practitioners Among Adults in Hungary: cross-Sectional Evaluation of Health Insurance Data. *Front. Pharmacol. 10*, 1-9, 2019.
   DOI: http://dx.doi.org/10.3389/fphar.2019.01280
   IF: 3.845 (2018)
2. **Harsha, N.**, Papp, M., Kőrösi, L., Czifra, Á., Ádány, R., Sándor, J.: Enhancing Primary Adherence to Prescribed Medications through an Organized Health Status Assessment-Based Extension of Primary Healthcare Services.
   Int. J. Environ. Res. Public Health. 16 (20), 1-13, 2019.
   DOI: http://dx.doi.org/10.3390/ijerph16203797
   IF: 2.468 (2018)

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List of other publications

3. **Harsha, N.**, Ziq, L., Giacaman, R.: Disability among Palestinian elderly in the occupied Palestinian territory (oPt): prevalence and associated factors.
BMC Public Health. 19 (1), 1-9, 2019.
DOI: http://dx.doi.org/10.1186/s12889-019-6758-5
IF: 2.567 (2018)

4. Kovács, N., Pálinkás, A., Sipos, V., Nagy, A., **Harsha, N.**, Kőrösi, L., Papp, M., Ádány, R., Varga, O., Sándor, J.: Factors associated with practice-level performance indicators in primary health care in Hungary: a nationwide cross-sectional study.
Int. J. Environ. Res. Public Health. 16 (17), 1-15, 2019.
DOI: https://doi.org/10.3390/ijerph16173153
IF: 2.468 (2018)

5. **Harsha, N.**, Ziq, L., Ghandour, R., Giacaman, R.: Well-being and associated factors among adults in the occupied Palestinian territory (oPt).
Health Qual. Life Outcomes. 14 (122), 1-7, 2016.
DOI: http://dx.doi.org/10.1186/s12955-016-0519-2
IF: 2.143

Total IF of journals (all publications): 13,491
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The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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