ABSTRACT

Purpose: Dissemination of generic drug (GD) use could provide significant savings on drug expenditures and contribute to the long-term sustainability of healthcare. We aimed to exhibit the nationwide trend of GD use in primary care and investigate potentially relevant drug and patient factors.

Methods: We analyzed all electronic prescriptions registered to national Prescription Information System by primary care physicians in Turkey during 2013-2016. We determined GD share in quantity and cost for each year. We further analyzed GD use in terms of patients' demographic characteristics, most commonly prescribed preparations, and frequent indications.

Results: In the four-year period, we identified 518,335,821 prescriptions, where GDs constituted 54.0% (n=786,972,813) with a total cost share of 36.9-37.8%. GD use was highest in 2016 (54.4%) and lowest in 2014 (53.6%). In each year, GD prescribing was higher in women (53.7-54.7%) than men (53.4-54.1%, $p<0.001$). GD utilization decreased as the age group increased, which was 64.0-64.5% in <18-year-old group and 46.0-47.1% in ≥75-year-old group. Among the top ten encountered indications, highest and lowest GD prescribing was detected in acute tonsillitis (68.1%) and hypertension (33.9). Metformin had the highest percentage of GD prescribing (96.1-97.7%) whereas esomeprazole showed the lowest GD prescribing (4.5-14.8%) among the most frequently used preparations in primary care.

Conclusions: This study shows a modest upward trend of GD utilization in primary care, though its share appears as lower than expected. GDs were less likely to be prescribed in older age groups and seem as more pronounced in acute conditions, particularly infectious diseases.

Keywords: primary care; prescribing; drug utilization

INTRODUCTION

The generic drug (GD) contains the active substance(s) with the same qualitative and quantitative composition as the reference drug and has the same/similar pharmaceutical form. For market approval, a candidate GD only requires demonstration of bioequivalence to the reference drug after patent expiration. No repetition of pre-clinical and clinical phase trials usually allows for cheaper pricing with the same therapeutic effect.[1] In fact, the price of GDs are reported as 20%-90% less than that of the reference drugs before the patent expires.[2] Therefore, disseminating GD use has been accepted as an effective approach to control increasing drug expenditures.[3] Furthermore, this provides significant savings on healthcare costs and contributes to the long-term sustainability of healthcare.[1,4]

It has been consistently shown that the effectiveness and safety of drugs do not differ between generic and reference preparations.[5-8] Despite huge evidence base, physicians, other healthcare professionals, and patients were often reported to have various concerns regarding the quality, efficacy, and safety of GDs as well as negative attitudes towards their use.[9-12] In fact, GD use is affected by many further factors, including demographic and clinical features of patients, variety of alternative options of drugs available for a given indication, prescribing with brand/generic name, and pharmacological properties of the drug, etc.[13-21]

Primary care prescriptions provide important insights about pharmacotherapy-focused subjects such as the drug utilization pattern of the majority of the population, overall clinical features and preferences of patients, and the prescribing behaviors of physicians. Primary care physicians exercise a fairly large volume of prescribing practice by initiating both the treatments of newly diagnosed patients and maintaining of those with chronic diseases. Therefore, generic or reference status of the drugs prescribed in primary care can provide important information about GD utilization pattern across the country. Apart from revealing the physician behavior in primary care, such findings will also lay the ground for the possible development areas in pharmacotherapy to make GD use more rational. In this study, we aimed to exhibit the nationwide trend of GD use in primary care and investigate potentially relevant drug and patient factors.

MATERIALS AND METHODS

In this cross-sectional study, all electronic prescriptions written by primary care physicians in Turkey between January 1, 2013 and December 31, 2016 were analyzed retrospectively. This prescription records was anonymized and obtained via Prescription Information System (PIS) managed by Turkish Medicines and Medical Devices Agency. The study was approved by Ethics Committee for Non-interventional Studies of Dokuz Eylul University (Approval No: 2019/05-32) and carried out in accordance with the principles in the Helsinki Declaration.

Drug-related data collected from prescriptions included Anatomical Therapeutic Classification (ATC) code, generic/reference drug status, route of administration (injectable/non-injectable), origin (domestic manufactured/imported), number of generic/reference drugs. Patient-related data included gender, age groups ("<18 years", "18-44 years", "45-64 years", "65-74 years", and "≥75 years"), and ICD-10 (International Classification of Diseases-10) diagnostic codes. The “GD prescribing rate” was calculated by dividing the number of GDs prescribed by the total number of generic and reference brands for each drug. In addition, the mean number of drugs per prescription (NDPP) for generic and reference drugs were determined.

The most frequently prescribed 20 active ingredients by year were listed and the number/percentages of the GDs were calculated. In addition, the number of reference and generic preparations for each of them on the market in the corresponding year were determined.

GD use was also determined in active ingredient groups with varying frequency of prescription: the most frequently prescribed preparations ranked as "1.-10.", "51.-60.", "101.-110.", "251.-260.", and "501.-510." were identified for the total study period and the number and rate of GDs prescribed specifically for each of these groups were examined.

The most frequently used drugs for specific indications were also identified to determine particular GD prescribing rates. This analysis was performed with single-diagnosis prescriptions (282.398.506), which constituted 54.5% of prescriptions, to make possible association of the drug(s) with the particular indications. The top ten frequent diagnoses in these single-diagnosis prescriptions were determined according to ICD-10 codes and GD use in these diagnoses was examined. In addition, prescriptions with certain other remarkable diagnoses [acute nasopharyngitis (J00), acute sinusitis (J01), depression (F32-F33), low back pain (M54.5), asthma (J45-J46), dyspepsia (K30), acute cystitis (N30.0), osteoarthritis (M15-M19), type 2

diabetes (E11-E14)] were further analyzed to determine GD number/percentages of thirty most commonly prescribed active ingredients for each indication.

In cost-related analyzes, the prices of generic and reference drugs were converted into Euro (€) currency. The PIS where drug prices were based on started to operate in 2010. The prices of drugs introduced to the market until this year were standardized at the currency of 2010. For the drugs that were licensed within the study period, standardization was made at the retail prices when they were first released. The mean cost of GDs in the prescriptions containing at least one GD were examined.

Statistical analysis

Statistical analyzes were done with GraphPad Prism 5.0 program. In this descriptive study, the data were expressed as numbers and percentages for categorical variables, and as mean and standard deviation for continuous variables. Chi-square test and t-test were used to compare categorical and continuous variables of the groups, respectively. Correlation analyzes were done with SPSS 25.0 software. An overall Type-1 error level of 5% was used to infer statistical significance.

RESULTS

In the four-year period covering 2013-2016, we identified 518,335,821 prescriptions, where GDs constituted 54.0% (n=786,972,813) and the remaining were reference drugs (46.0%, n=670,061,457). In each year, GDs were prescribed more frequently and this rate was lowest in 2014 (53.6%) and highest in 2016 (54.4%). The annual mean "NDPP for GDs and reference drugs ranged from 1.51±1.17 to 1.53±1.16 and 1.27±1.14 to 1.31±1.14, respectively (Supplement 1).

In total, GDs constituted 54.2% and 53.8% of the drugs prescribed to women and men, respectively. In each of the years examined, GD prescribing was higher in women (53.7%-54.7%) than men (53.4%-54.1%, $p<0.001$), (Figure 1). GD use declined as the age group increased from 64.0%-64.5% in <18-year-old population to 46.0%-47.1% in ≥75-year-old population ($p<0.001$) for each year (Supplement 1), which was also preserved during the entire study period (Figure 2).

GDs were frequently prescribed in both the "injectable" and "non-injectable" drug groups (53.1%-56.2% and 53.6%-54.4%, respectively), (Supplement 2). During the study period 97.7%-97.9% of GDs were found to be domestically manufactured. The mean NDDP varied between 1.48±1.16 and 1.49±1.18 for domestic GDs.

The total cost of the drugs prescribed in the primary care for four years was €24.08 billion. GDs accounted for 37.4% of the total cost (range: 36.9%-37.8%), (Figure 3). The mean annual cost of all drugs was €6.02 billion (range: €4.81-€6.71 billion), and GDs costed an average of €2.25 billion (range: €1.82-€2.53 billion). Prescriptions containing at least one GD constituted 80.0% of all prescriptions (range: 79.8%-80.4%), (Supplement 3).

GD use was predominant in the top 10 (71.0%) and 51-60. most frequently prescribed active ingredient groups (54.0%), whereas reference preparations were prescribed more frequently (65.7%-79.0%) in lower-order groups (Figure 4). Active ingredients in the top 10 group were found to form 25.8% of all prescribed drugs, the GDs prescribed in this group accounted for 33.9% of all GDs, which was 16.3% for reference drugs.

Among the most frequently prescribed preparations with at least one generic and reference brand, metformin (96.1%-97.7%), etodolac (88.3%-89.4%), and pantoprazole (84.4%-86.6%) were the top three active ingredients with highest rate of GD prescribing. Active ingredients with lowest generic prescription rates were esomeprazole (4.5%-14.8%), naproxen (11.9%-14.4%), and metoprolol (14.9%-24.4%), (Table 1). We found no correlation between GD rate in the market and GD prescribing for any of the year (r: 0,448; 0,507; 0,458; 0,490 in between 2013-2016, respectively; $p>0.05$).

In the top ten most frequently encountered diagnoses, GD prescribing was higher in all indications (highest in acute tonsillitis as 68.1%) except “essential hypertension” (33.9%) and “general medical examination” (48.1%), (Table 2). For specific indications, GD prescribing was higher in infectious (63.8-65.3%) and several non-infectious diseases (low back pain, osteoarthritis, and type 2 diabetes) but lower in depression (41.4%), asthma (42.2 %), and dyspepsia (44.7%), (Figure 5).

DISCUSSION

We examined >500 million primary care prescriptions where GDs had a share of 54% in quantity and 37% in cost. While this could be lower than expected, it is noticeable that GD prescribing exhibit a modest upward trend. Other remarkable findings include the consistent reduction of GD prescribing towards older age groups and relative increase in acute conditions, particularly infectious diseases.

GD utilization varies between countries, especially with the effect of different government policies. The share of GDs range from 17% to 83% across Europe, 84% in the USA, %68.6% in Canada and 56.2% in Japan.[22,23] This sales volume was reported to vary between 53.6% to 56.6% in Turkey with an increasing trend but still behind that of many OECD countries.[24,25] This increase trend across the country seems to be compatible with GD use in primary care in our study. However, the fact that 20% of the prescriptions did not contain GDs indicates the need for investigating underlying causes as this modest increase appears as not sufficient and should be improved. In fact, spreading GD use is an important strategic step in reducing health expenditures. In Europe, policies was developed between 2008 and 2015 where increasing GD use was aimed to decrease drug expenditures by making it compulsory to prescribe drugs with active substance names in many countries such as Belgium, Greece, and Spain.[22,26] In a circular issued by the Turkish Ministry of Health in 2009 and re-addressed afterwards if required, it was emphasized that it is not scientifically and legally valid for physicians to write on prescriptions that pharmacists should not substitute reference drugs with GDs.[27] This situation indicates somehow an unsatisfactory level of physicians' adoption for GD prescribing and may have contributed to the limited increase in the study period. On the other hand, the dissemination and promotion of GD use has been incorporated in the 2018-2022 Action Plan of the health authority regarding rational use medicines.[28] In this context, our findings might serve as a baseline for further studies that would examine the impact of this intervention.

Among potential patient factors effective on GD use, we did not observe a profound impact of gender -albeit mildly higher in women- whereas age appears as an important parameter affecting GD use. While GDs constituted near two-thirds of all drugs in children, it has been observed that this trend decreased as the age got older and reference drugs became predominant over the age of 65 years. Higher use of GDs in younger patients might be partially associated

with their clinical conditions for which the drugs are indicated, e.g. relative dominance of infectious diseases in younger individuals.[29] In fact, the GD rate (63% - 68%) detected in acute diagnoses in our study, was in parallel with the higher rate of generics of antibiotics prescribed in infectious diseases. It was reported that 66.5% of prescribed antibiotics for acute infections in primary care in Turkey was GDs and its use was highest (66%) in acute pharyngitis.[30] Similarly, GDs formed 66% of all drugs in this indication in our study. On the other hand, it has been shown in several studies that there is a prejudgment towards GDs in the elderly patient group, where we found low use of GDs.[20,31,32] This may have affected the prescribing behavior of physicians.[33] In addition, the difference in GD prescribing behavior in chronic diseases that increase with age may partially explain the decreasing trend related to age. It was reported that the use of GDs in patients with multiple chronic diseases was lower than those without, and patients with chronic diseases may have a negative attitude towards GDs.[34-36] Furthermore, such unfavorable attitudes were reported to affect physicians' prescribing with a tendency to reference drugs increased with comorbidity and older age.[37] Consistently, up to 79% of physicians were reported to prefer reference drugs for their patients with some medical conditions including cardiovascular diseases.[38] This was further supported by the lower GD use in chronic conditions in our study, including hypertension (34%), depression (41%), and asthma (42%). In particular, GD use was reported to vary 35% to 45% in hypertension, making the performance of our physicians lower than expected.[39-40] This might be partly explained by the fact that about 80% of metoprolol, the only antihypertensive agent among the top used agents, was prescribed as generic. Given the increase in chronic care expenditures, it seems crucial GD use be encouraged in chronic diseases that increase with age in reducing drug-related costs.[41,42] In fact, using GDs in the treatment of cardiovascular diseases and diabetes has been reported to reduce healthcare expenditures.[42,43] Considering the raising share of chronic disease management in primary care, the findings in our study emphasize that one of the prioritized addresses of activities to promote GD use is primary care physicians.

GDs have generally lower costs than reference drugs. The average price of a reference drug in Turkey was reported to be >3-fold of that for GDs.[44] In our study, GDs constituting 54% of the drugs, had a 37% share in cost. In 2017, the average GD sales volume of 26 OECD member countries was reported to be 52% and its share was 25%.[25] On the other hand, this rate is higher in the USA and it is reported that generics, which make up 89% of the drugs prescribed in

2016, constitute 26% of the total prescription cost.[45] In this context, our findings on GD use might be suggested as partially satisfactory in the primary care. Efforts to encourage and increase GD use were reported that drug expenditures were reduced by 61% in the European Union countries with a saving of approximately €100 billion in 2014.[4] This tends to justify enhancement of GD-focused interventions in the primary care for a sustainable healthcare service.

Generic market competition is an expected phenomenon in frequently used drug groups. In fact, we observed about 70% share of GDs for the top 20 most frequently prescribed preparations. This value fell below the country average after the first 60 drugs that were most often prescribed, leaving the reference drugs as predominant gradually. On the other hand, no association was detected between a drug's GD availability and GD prescribing percentage for the commonly used preparations. This does not seem to confound our findings regarding the impact of age and clinical indication on GD use.

GD use by pharmaceutical forms showed the similar pattern as overall with a very modestly higher use for injectable drugs albeit with a fluctuating course. While we may suggest that pharmaceutical form does not appear to affect GD use, this needs to be further investigated by qualitative and/or quantitative studies focused on the various forms of the drugs. On the other hand, we observed 97% of GDs to be domestic-manufactured in the primary care. This was consistent with the previous reports of the overall domestic share of GDs in the country, which may be attributed to the accredited authorized role of the health authority in monitoring and auditing Good Manufacturing Practices internationally.[46]

The percentage of prescribing drugs with generic name in prescriptions is one of the indicators of rational drug use and increase use of GDs.[47] This practice is exercised in many countries with different strategies. A USA study reported that prioritization of generic-brands during browsing of physicians for drugs in electronic prescribing increased GD share in prescriptions.[48] In addition, this was reported to be further contributed by prescribing with generic names rather than brands.[49]

In this study, GD prescribing patterns of physicians were evaluated. Therefore, the main limitation of the study could be its retrospective design since we could not assess the actual utilization of the generic or reference drug by patients, including the conditions and changes during its dispending at the pharmacy or reimbursement level. In this descriptive study, the

relationship between diagnosis and treatment was not established and drug/diagnosis details were not evaluated by their demographic groups. In addition, for minimizing confounding indications, prescriptions with multiple diagnoses were not assessed for indication-oriented GD use, which can be considered as another limitation of the study. Finally, the cost analyses of the study should be interpreted considering that the currency conversion of Turkish Lira to Euro was not performed on actual time, rather on a standardized year.

In conclusion, the extent of GD utilization in primary care facilities in Turkey has been presented for the first time with a holistic perspective and with the trend of change over the years. This study shows a modest upward trend of GD utilization in primary care, though its share appears as lower than expected. GDs were less likely to be prescribed in older age groups and seem as more pronounced in acute conditions, particularly infectious diseases. Primary care physicians are typically more likely to provide health care for patients of all ages, a larger population, and diversity than other physicians in a given time period. Therefore, the contribution of primary care physicians to the efforts that aim to increase GD use and thus to drug-based cost savings will be considerably significant. The striking points obtained from this research not only introduces a perspective on GD use in primary care, but also give important clues in critical aspects for the dissemination of GD use.

Ethics Statement

The study was approved by Ethics Committee for Non-interventional Studies of Dokuz Eylul University (Approval No: 2019/05-32).

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Conflict of interest

The authors declare that there is no conflict of interest.

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Data availability statement

The data that support the findings of this study are available from thecorresponding author upon reasonable request.

REFERENCES

1- Sacks CA, Lee CC, Kesselheim AS, Avorn J. Medicare spending on brand-name combination medications vs their generic constituents. JAMA. 2018;320(7):650-656.

2- Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacol Toxicol. 2013;14:1.

3- Cameron A, Laing R. Cost savings of switching private sector consumption from originator brand medicines to generic equivalents. World health report, 2010;35:210-5.

4- IMS Institute for Healthcare Informatics. The role of generic medicines in sustaining healthcare systems: a european perspective. 2015. https://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS_Health_2015_-_The_Role_of_Generic_Medicines_in_Sustaining_Healthcare_Systems_-_A_European_Perspective.pdf. Published June, 2015. Accessed September 11, 2020.

5- Manzoli L, Flacco ME, Boccia S, et al. Generic versus brand-name drugs used in cardiovascular diseases. Eur J Epidemiol. 2016;31(4):351-368.

6- Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med. 2014;161(6):400-407.

7- Kesselheim AS, Misono AS, Lee JL, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA. 2008;300(21):2514-2526.

8- Desai RJ, Sarpatwari A, Dejene S, et al. Comparative effectiveness of generic and brand-name medication use: A database study of US health insurance claims. PLoS Med. 2019;16(3):e1002763.

9- Colgan S, Faasse K, Martin LR, et al. Perceptions of generic medication in the general population, doctors and pharmacists: a systematic review. BMJ Open. 2015;5:e008915.

10- Shrank WH, Liberman JN, Fischer MA, et al. Physician perceptions about generic drugs. Annals of Pharmacotherapy. 2011;45(1):31-38.

11- Chong CP, Hassali MA, Bahari MB, et al. Exploring community pharmacists' views on generic medicines: a nationwide study from Malaysia. Int J Clin Pharm. 2011;33(1):124-131

12- Dunne SS, Dunne CP. What do people really think of generic medicines? A systematic review and critical appraisal of literature on stakeholder perceptions of generic drugs. BMC Med. 2015;13:173.

13- Howard JN, Harris I, Frank G, Kiptanui Z, Qian J, Hansen R. Influencers of generic drug utilization: a systematic review. Res Social Adm Pharm. 2018;14(7):619-627.

14- Kesselheim AS, Eddings W, Raj T, et al. Physicians' trust in the FDA's use of product-specific pathways for generic drug approval. PLoS One. 2016;11(10):e0163339.

15- Lewek P, Smigielski J, Kardas P. Factors affecting the opinions of family physicians regarding generic drugs--a questionnaire based study. Bosn J Basic Med Sci. 2014;15(1):45-50.

16- Mondelo-García C, Mendoza E, Movilla-Fernández MJ, Coronado C. Perceptions of pharmacists and physicians on generic substitution in a financial crisis context in Northwestern Spain: a qualitative study. Health Policy. 2018;122(12):1316-1325.

17- Liou WS, Hsieh SC, Chang WY, Wu GH, Huang HS, Lee C. Brand name or generic? What are the health professionals prescribed for treating diabetes? A longitudinal analysis of the National Health Insurance reimbursement database. Pharmacoepidemiol Drug Saf. 2013;22(7):752-759.

18- Fabiano V, Mameli C, Cattaneo D, et al. Perceptions and patterns of use of generic drugs among Italian family pediatricians: first round results of a web survey. Health Policy. 2012;104(3):247-252.

19- Quintal C, Mendes P. Underuse of generic medicines in Portugal: an empirical study on the perceptions and attitudes of patients and pharmacists. Health Policy. 2012;104(1):61-68.

20- Shrank WH, Cox ER, Fischer MA, Mehta J, Choudhry NK. Patients' perceptions of generic medications. Health Aff (Millwood). 2009;28(2):546-556.

21- Tachi T, Saito K, Esaki H, et al. Medical and economic factors influencing generic drug use in the Japanese public health system: influencing factors in different populations. Int J Health Plann Manage. 2018;33(2):489-501.

22- Wouters OJ, Kanavos PG, McKEE M. Comparing generic drug markets in Europe and the United States: prices, volumes, and spending. Milbank Q. 2017;95(3):554-601.

23- Kuribayashi R, Appleton S. Comparison of generic drug reviews for marketing authorization between Japan and Canada. Drugs R D. 2017;17(3):371-379.

24- Republic of Turkey Ministry of Health. Health Statistic Yearbook 2017, Ankara; 2018. Republic of Turkey Ministry of Health General Directorate of Health Information Systems. https://dosyasb.saglik.gov.tr/Eklenti/30148,ingilizcesiydijiv1pdf.pdf?0. Accessed September 11, 2020.

25- Organisation for Economic Co-operation and Development (OECD), Health at a Glance 2019. OECD Indicators, OECD Publishing, Paris. https://doi.org/10.1787/4dd50c09-en.

26- Panteli D, Arickx F, Cleemput I, et al. Pharmaceutical regulation in 15 European countries: review. Health Syst Transit. 2016;18(5):1-122.

27- Republic of Turkey Ministry of Health. Generic drug utilization. Circular numbered 430181. 18.06.2009. www.istanbuleczaciodasi.org.tr/upload/pdf/20090618_es_deger_ilac.pdf. Accessed September 11, 2020.

28- Republic of Turkey Ministry of Health. 2018-2022 Strategic Plan. https://titck.gov.tr/storage/Archive/2018/dynamicModulesAttachment/884b5ed7-8b2d-4646-b7a3-1c6914c3aa89.pdf. Accessed September 11, 2020.

29- Global Burden of Disease Pediatrics Collaboration. Global and National Burden of Diseases and Injuries Among Children and Adolescents Between 1990 and 2013: Findings From the Global Burden of Disease 2013 Study. JAMA Pediatr. 2016;170(3):267–287.

30- Mollahaliloglu S, Alkan A, Donertas B, Ozgulcu S, Akici A. Assessment of antibiotic prescribing at different hospitals and primary health care facilities. Saudi Pharm J. 2013;21(3):281-291.

31- Iosifescu A, Halm EA, McGinn T, Siu AL, Federman AD. Beliefs about generic drugs among elderly adults in hospital-based primary care practices. Patient Educ Couns. 2008;73(2):377-383.

32- Heikkilä R, Mäntyselkä P, Ahonen R. Do people regard cheaper medicines effective? Population survey on public opinion of generic substitution in Finland. Pharmacoepidemiol Drug Saf. 2011;20(2):185-191.

33- Toklu HZ, Dülger GA, Hıdıroğlu S, et al. Knowledge and attitudes of the pharmacists, prescribers and patients towards generic drug use in Istanbul – Turkey. Pharmacy Practice 2012;10(4):199-206.

34- Hassali MA, Kong D, Stewart K. Generic medicines: perceptions of consumers in Melbourne, Australia. International Journal of Pharmacy Practice. 2005;13(4):257-264.

35- Himmel W, Simmenroth-Nayda A, Niebling W, et al. What do primary care patients think about generic drugs?. Int J Clin Pharmacol Ther. 2005;43(10):472-479.

36- Chong CP, March G, Clark A, Gilbert A, Hassali MA, Bahari MB. A nationwide study on generic medicines substitution practices of Australian community pharmacists and patient acceptance. Health Policy. 2011;99(2):139-148.

37- Beauvais V, Marque A, Ferté G, et al. Factors influencing the use of the “not for generic substitution” mention for prescriptions in primary care: a survey with general practitioners. BMC Health Serv Res. 2018;18(1):850.

38- Villarroel-Stuart AR. Investigation of the National Drug Lists and the Perception of Pharmacists and Physicians about Generic Drugs at Health Institutions in the North Central Region of Trinidad. West Indian Med J. 2019. doi: 10.7727/wimj.2018.014.

39- Corrao G, Soranna D, Arfè A, et al. Are generic and brand-name statins clinically equivalent? Evidence from a real data-base. Eur J Intern Med. 2014;25(8):745-750.

40- Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Medication adherence and use of generic drug therapies. Am J Manag Care. 2009;15(7):450-456.

41- Busse R, Blümel M. Tackling chronic disease in Europe: strategies, interventions and challenges. No. 20. World Health Organisation, 2010.

42- Shrank WH, Choudhry NK, Liberman JN, Troyen A. Brennanet al. The use of generic drugs in prevention of chronic disease is far more cost-effective than thought, and may save money. Health affairs. 2011;30(7):1351-1357.

43- Gellad WF, Donohue JM, Zhao X, et al. Brand-name prescription drug use among Veterans Affairs and Medicare Part D patients with diabetes: a national cohort comparison. Ann Intern Med. 2013;159(2):105-114.

44- Pharmaceutical Industry Employers' Association. Turkey pharmaceutical industry report 2018. http://ieis.org.tr/ieis/tr/sektorraporu2018. Published 2019. Accessed September 11, 2020.

45- Association for Accessible Medicines. Generic Drug Access and Savings in the US. 2017. https://accessiblemeds.org/sites/default/files/2017-07/2017-AAM-Access-Savings-Report-2017-web2.pdf. Published 2017. Accessed September 11, 2020.

46- Pharmaceutical Industry Employers' Association. Turkey pharmaceutical industry report 2017.
http://ieis.org.tr/ieis/assets/front/sektorraporu2017/Turkiye_Ilac_sektoru_2017_Raporu.pdf.
Published 2018. Accessed September 11, 2020.

47- World Health Organization. Regional Office for Europe, Dukes MNG. Drug utilization studies: methods and uses. World Health Organization. Regional Office for Europe. 1993. https://apps.who.int/iris/handle/10665/260517. Accessed September 11, 2020.

48- Malhotra S, Cheriff AD, Gossey JT, Cole CL, Kaushal R, Ancker JS. Effects of an e-Prescribing interface redesign on rates of generic drug prescribing: exploiting default options. J Am Med Inform Assoc. 2016;23(5):891-898.

49- Appleby J. The rise and rise of generic prescribing. BMJ. 2015;351:h5507.

TABLES

Table 1. The reference and generic status parameters of the top 20 prescribed preparations by years.

Drug (ATC) / Years	2013				2014				2015				2016			
	Rank	Drug Product		Generic Drug n (%)	Rank	Drug Product		Generic Drug n (%)	Rank	Drug Product		Generic Drug n (%)	Rank	Drug Product		Generic Drug n (%)
		R	G			R	G			R	G			R	G	
Other cold preparatıons (R05X)	**1**	15	83	15.565.669 (67.2)	**1**	13	57	19.526.820 (70.5)	**1**	13	60	18.760.031 (71.2)	**1**	13	61	19.849.375 (73.5)
Amoxicillin and enzyme inhibitor (J01CR02)	**2**	11	58	7.517.282 (61.5)	**2**	11	48	8.112.548 (59.2)	**2**	11	49	8.110.196 (61.6)	**2**	10	47	8.163.799 (59.9)
Diclofenac (M01AB05)	**3**	11	32	7.509.905 (77.6)	**3**	11	18	9.086.150 (78.1)	**3**	11	20	8.632.458 (79.4)	**4**	11	19	8.927.577 (80.8)
Paracetamol (N02BE01)	**4**	4	60	6.841.644 (71.6)	**4**	4	32	8.059.438 (72.1)	**4**	4	28	7.621.211 (71.6)	**3**	5	23	7.982.833 (69.6)
Lansoprazole (A02BC03)	**5**	0	34	5.897.327 (100.0)	**5**	0	35	6.395.227 (100.0)	**7**	0	33	5.469.175 (100.0)	**9**	0	30	5.227.879 (100.0)
Acetylcysteine (R05CB01)	**6**	1	68	5.603.983 (99.7)	**7**	1	46	5.836.349 (99.8)	**9**	1	48	5.241.551 (100.0)	13	0	49	4.897.917 (100.0)
Dexketoprofen (M01AE17)	**7**	10	28	1.486.414 (27.6)	**6**	3	21	1.655.758 (27.2)	**8**	3	27	1.485.790 (27.3)	**7**	3	24	1.630.743 (29.1)
İbuprofen (M01AE01)	**8**	7	31	4.215.142 (81.0)	**9**	6	12	4.559.475 (82.2)	**6**	7	12	4.581.494 (83.2)	**6**	5	16	4.657.838 (81.3)
Thiocolchicoside (M03BX05)	**9**	5	36	3.605.828 (71.9)	12	5	36	3.781.007 (72.6)	14	5	41	2.922.471 (72.0)	22	5	47	2.310.514 (75.2)
Acetylsalicylic acid (B01AC06)	**10**	3	10	1.548.558 (33.2)	**8**	3	6	1.900.931 (32.6)	**5**	3	6	1.971.689 (33.0)	**5**	3	5	2.208.209 (33.9)
Various (A01AD11)	11	2	22	4.477.986 (96.3)	**10**	2	27	5.292.063 (96.6)	11	2	26	4.878.681 (96.6)	**8**	2	31	5.158.869 (96.9)
Pantoprazole (A02BC02)	12	4	39	3.852.831 (86.6)	11	3	33	4.684.323 (85.7)	**10**	3	35	4.317.311 (85.4)	**10**	3	36	4.409.309 (84.4)
Paracetamol comb.[a] (N02BE51)	13	6	32	2.293.341 (54.8)	17	6	18	2.448.175 (55.8)	16	6	20	2.177.287 (57.0)	18	7	22	2.181.316 (60.0)
Flurbiprofen (M01AE09)	14	1	25	4.140.981 (99.9)	14	0	16	4.516.491 (100.0)	20	0	16	3.519.696 (100.0)	21	0	16	3.003.166 (100.0)
Etodolac (M01AB08)	15	1	30	3.492.369 (89.2)	18	1	19	3.835.216 (89.4)	19	1	19	3.147.357 (89.3)	20	1	20	2.684.207 (88.3)
Vitamin B1 comb.[b] (A11DB)	16	4	27	1.424.961 (36.7)	16	4	13	1.598.301 (35.9)	15	4	12	1.464.248 (36.3)	14	3	10	1.460.020 (35.6)
Butamirate (R05DB13)	17	4	12	2.557.566 (69.7)	15	4	10	3.216.081 (71.7)	13	4	16	3.453.846 (75.6)	12	5	16	4.062.028 (82.8)
Cefuroxime (J01DC02)	18	12	78	2.763.598 (80.2)	22	9	43	2.833.598 (78.2)	25	9	44	2.298.625 (80.2)	32	9	44	1.985.362 (81,8)
Metformin (A10BA02)	19	3	23	3.264.065 (97.7)	13	2	17	4.432.090 (96.8)	12	2	20	4.502.473 (96.8)	11	2	21	4.904.285 (96.1)
Naproxen (M01AE02)	20	8	39	455.258 (14.4)	23	8	21	457.006 (12.9)	23	8	19	380.144 (12.6)	26	8	16	325.969 (11.9)
Metoprolol (C07AB02)	23	7	9	428.243 (14.9)	19	7	8	674.663 (18.1)	17	7	7	826.223 (21.8)	15	7	12	993.684 (24.4)
Imidazoles/triazoles in comb. with corticosteroids (D01AC20)	22	1	5	2.179.289 (73.1)	20	2	6	2.726.081 (75.4)	21	1	7	2.663.450 (77.1)	17	1	9	2.920.864 (79.6)
Esomeprazole (A02BC05)	24	6	8	128.148 (4.5)	21	5	4	350.735 (9.7)	18	5	9	526.662 (14.7)	16	5	11	542.654 (14.8)
Oxymetazoline (R01AA05)	27	3	5	907.817 (38.0)	26	3	2	1.073.447 (36.9)	24	3	2	961.685 (33.1)	19	3	3	1.048.967 (32.6)
First 20 Drug Generic Subtotal				88.514.708 (70.7)				102.337.187 (71.0)				93.609.850 (69.8)				93.912.373 (68.5)
Other Generic Drugs				89.795.204 (43.9)				105.706.142 (43.3)				103.423.349 (44.7)				109.674.000 (46.3)
Total Generic Drug				178.309.912 (54.1)				208.043.329 (53.6)				197.033.199 (53.9)				203.586.373 (54.4)

R, reference drug, G, generic drug; a, except psycholeptics; b, Combinations with Vitamins B6 and B12; comb:combination

Table 2. Generic drug use for the top 10 diagnoses encountered in the single-diagnosis prescriptions of the primary care by years.

Year	2013		2014		2015		2016		2013-2016	
Diagnosis (ICD-10)	**Diagnosis rank**	**Generic Drug n (%)**	**Diagnosis**	**Generic Drug n (%)**	**Diagnosis**	**Generic Drug n (%)**	**Diagnosis rank**	**Generic Drug n (%)**	**Diagnosis rank**	**Generic Drug n (%)**
Acute upper respiratory infection, unspecified (J06.9)	**1**	6.337.676 (66.3)	**2**	8.252.215 (66.3)	**2**	8.051.440 (66.5)	**2**	8.984.725 (66.9)	**2**	31.626.056 (66.5)
Acute pharyngitis, unspecified (J02.9)	**2**	6.208.331 (66.1)	**3**	7.168.137 (66.5)	**3**	6.196.689 (66.6)	**3**	6.031.152 (67.3)	**3**	25.604.309 (66.6)
Essential hypertension (I10)	**3**	1.641.225 (29.7)	**1**	4.073.153 (34.5)	**1**	3.410.942 (34.0)	**1**	3.982.946 (35.4)	**1**	13.108.266 (33.9)
Acute pharyngitis (J02)	**4**	5.050.367 (66.7)	**4**	6.331.463 (66.0)	**4**	5.681.361 (66.3)	**5**	5.578.262 (66.6)	**4**	22.641.453 (66.4)
Acute nasopharyngitis [common cold], (J00)	**5**	3.349.883 (62.4)	**5**	4.870.798 (62.6)	**5**	4.390.208 (62.9)	**4**	4.796.548 (63.9)	**5**	17.407.437 (63.0)
Acute tonsillitis, unspecified (J03.9)	**6**	3.725.542 (68.2)	**7**	4.104.348 (67.9)	**7**	3.463.976 (68.2)	**7**	3.534.191 (68.1)	**6**	14.828.057 (68.1)
Acute tonsillitis (J03)	**7**	3.469.839 (68.5)	**6**	4.205.965 (67.4)	**6**	3.560.292 (68.2)	**6**	3.590.625 (67.8)	**7**	14.826.721 (67.9)
Other general examination (Z00.8)	**8**	1.318.849 (58.8)	(30)	-	(57)	-	(42)	-	(23)	-
Gastroesophageal reflux disease (K21)	**9**	967.947 (52.0)	**9**	2.250.306 (52.1)	**9**	1.744.080 (53.2)	**9**	1.917.917 (53.6)	**9**	6.880.250 (52.8)
Gastro-esophageal reflux disease without esophagitis (K21.9)	**10**	820.473 (53.6)	(11)	-	(12)	-	(13)	-	(11)	-
Myalgia (M79.1)	(11)	-	**8**	2.728.833 (55.7)	**8**	2.183.127 (56.5)	**8**	2.421.565 (57.1)	**8**	8.594.638 (56.9)
General medical examination (Z00.0)	(15)	-	**10**	2.207.764 (47.5)	**10**	1.679.682 (47.9)	**10**	1.901.511 (48.6)	**10**	6.742.985 (48.1)
First 10 Diagnosis Total[a]		32.890.132 (61.4)		46.192.982 (58.8)		40.361.797 (59.4)		42.739.442 (59.6)		162.260.172 (59.6)

ICD: International Classification of Diseases; a, Drugs related to the diagnoses that are not included in the top 10 diagnoses in the diagnosis order, though given in the table, were not included in the total.