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LEGAL AND ECONOMIC IDENTIFICATION AND ASSESSMENT OF PHARMACY SUBSTITUTION IN NARROW THERAPEUTIC INDEX DRUGS, ON THE EXAMPLE OF EPILEPTIC MEDICATIONS IN POLAND

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Abstract: Currently in Poland, there is neither regulation aiming at framing the complexity of substitution process arising at the pharmacy level, nor further guidelines depending on the drug category. FDA describes a narrow therapeutic index drug (NTI) in the 21 Code of Federal Regulations 320.33(c) and highlights that safe and effective use of such drug products require careful titration and patient monitoring. In major therapeutic areas disadvantages of the generic substitution are irrelevant or minor in comparison to the economic benefit. In epilepsy, a number of experts and professional bodies have recommended caution with generic substitution of drugs used in this condition. The aim of the study is to legally and economically identify and assess drug substitution occurrence in Polish background among selected narrow therapeutic index drugs used in epilepsy. Paper is divided into two sections: first is retrospective based and tackles the data received from the National Health Fund; whereas second section takes under consideration questionnaire based results gained during medical history being collected with the patients. Basing on most commonly substituted substance in epilepsy: carbamazepine, the maximum single difference in cost in substitution at the pharmacy was identified around the level of 1.7 PLN, and maximum extra pay at the same level. Observed/reported changes, ADRs, discomfort were provided based on the questionnaire. The study highlights the necessity of planning process and evaluation of current market regulations.

Keywords: pharmacy substitution, carbamazepine, pharmacy law

European Union law has not imposed on Member States a strictly defined reimbursement policy about medical product substitution, because it has presumed that each Member State has its own domestic law on medical product substitution in place (1). Nowadays in Europe, there are many reimbursement systems, and they vary considerably in their permissions, prohibitions, and penalties. A general aim of reimbursement policies is to increase the share for generic drugs in the medical products market (2, 3).

Polish pharmaceutical law (according to Art. 44 of the law of 12 May 2011 on the reimbursement of medicines, food products of special nutritional purpose and medicinal products) requires pharmacists to provide patients with information on less expensive reimbursed drugs, if they are available, and there is an obligation to dispense the alternatives if the patient so wishes. This is called pharmacy substitution. Substitution is a process of switching the prescribed pharmaceutical product with an available equivalent. It arises in the pharmacy between a pharmacist or a pharmacy technician and a patient, with the indirect participation of a medical doctor physician and, in terms of the reimbursement of pharmaceuticals, commonly it also involves the public purse. The scope of substitution includes both branded and generic medical products. Article 15 of the Pharmaceutical Act defines an equivalent drug (i.e., a generic drug) as a product with the same

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qualitative and quantitative composition, and the same pharmaceutical form as the reference drug, and in which the bioequivalence to the reference product has been confirmed by bioavailability tests. Salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives of an authorized active ingredient substance must be the same active substance (4).

Pharmaceutical law states sine qua non criteria for appropriate substitution: both products must have the same international name and dose, a pharmaceutical form that does not give rise to therapeutic differences, preserves the same therapeutic indication, and a retail price which should not exceed the public fund financing limit. Substitution also requires the patient's permission. According to Polish pharmaceutical law, a physician's permission is not needed. In some other countries e.g. in the Czech Republic and in The Netherlands the requirement for a physician's permission plays a key role in substitution policies. It is possible that the permission of a physician could be written in a special statement to the pharmacist (5).

In 2016 short comment about the safety of generic substitution in epilepsy occurred (6). It commented on the position of Medicines and Healthcare products Regulatory Agency from the United Kingdom, which initiated the introduction (with the Commission on Human Medicines) of special categories for drug substitution with such medicines. MHRA writes on the governmental website: "Different antiepileptic drugs (AEDs) vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers' products of a particular drug may cause adverse effects or loss of seizure control. AEDs have been divided into three risk-based categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product" (7, 8). For category 1 (carbamazepine, phenobarbital, phenytoin, and primidone) it is understood, that the patient should not be substituted with the various versions (understood as a different manufacturer) of the drug but kept on one version. For category 2, a doctor should decide, together with the patient whether it is not a problem to substitute between the various versions of the drug. For category 3 (in example levetiracetam), a patient can be substituted for a different version of a drug. The guidance indicates how to write the prescription in order to ensure consistency of supply for a patient, what in terms of avoidance of automatic substitution (especially for categories 1 and 2) at the pharmacy level is crucial.

FDA describes a narrow therapeutic index drug (NTI) in the 21 Code of Federal Regulations 320.33(c) and highlights that safe and effective use of such drug products require careful titration and patient monitoring (8, 9); and carbamazepine (mostly used by Polish patients as study of this paper results) is classified as one of such substances.

In this paper authors continue work in the subject of drug substitution (4, 10, 11), focusing on the field of neurological drugs, especially used in epilepsy. Paper is divided into two sections: first is retrospective based and tackles the data received from the National Health Fund; whereas second section takes under consideration questionnaire based results gained during medical history being collected with the patients.

Table 1. Questionnaire of the drug substitution filled by the medical doctors while collecting medical history of the patient.

No.	Question	Answer
1.	Was the antiepileptic drug substituted in pharmacy (for containing the same INN and dose) since patients' last visit in doctors' office?	Yes/No
2.	If yes, please fill in the trade name for the antiepileptic drug being used so far, and for the new antiepileptic, which was dispensed in pharmacy.	To fill in
3.	Did the patient observe/report changes in the efficacy of the undertaken therapy?	Yes/No If Yes - to fill in
4.	Did the patient observe/report adverse reactions of the dispensed (substituted) drug?	Yes/No If Yes - to fill in
5.	Did the patient observe/report discomfort in the usage of dispensed (substituted) drug?	Yes/No If Yes - to fill in
6.	Do You as medical doctor use the "dispense as written" notation?	Yes/No
7.	Are the decisions concerning substitution of antiepileptic drugs for Your patients consulted with You before they are made?	Yes/No
8.	Is the health condition of Your patients monitored after the substitution being made in pharmacy?	Yes/No

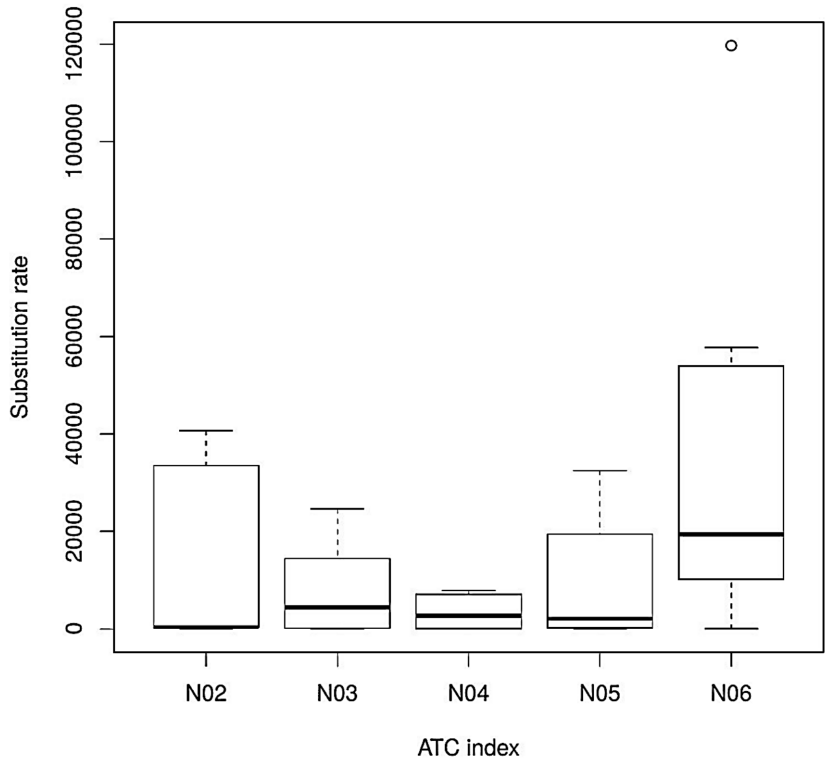


Figure 1. Kruskal-Wallis rank sum test for Table 2

Aim of the study

The aim of the study is to legally and economically identify and assess drug substitution occurrence in Polish background among selected narrow therapeutic index drugs used in epilepsy. It is assumed that Polish patients undergo drug substitution with the antiepileptic drugs. It is expected that such drug substitution does not bring significant economic benefits to the patients.

Methods

The manuscript is divided into two sections of results, according to which different statistical methods were obtained.

Section 1. Retrospective data based

Since the Reimbursement act being in force (2012), Polish pharmacies are obliged to report to the National Health Fund (NHF) data concerning dispensed (based on prescription) medicines. For the purpose of scientific work, such data were obtained from the NHF and the retrospective study was performed. Received data covered a four-year period (2012-2015) and contained a list of medicines as prescribed-dispensed in the form of EAN codes (European Article Number). Because the scientific work is in the subject of drug substitution the data contained only positions with different EANs as prescribed-dispensed. The obtained data did not cover the name of the substance; for reaching this, EANs were swapped for the recommended International Nonproprietary Names (rINNs) from the publicly available lists (yearly available) of all market-authorized medicines of the Office for the Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland. All the substances were categorized into the ATC classification (Table 2) using Microsoft Excel from Microsoft Office 365 (Microsoft Corp., Redmond, WA, USA) sorting tools and the template of Pharmacopeia. The substitution of neurological ATC groups N02, N03, N04, N05, N06 were given a Kruskal-Wallis rank sum test (Fig. 1).

Four substances: carbamazepine, phenobarbital, phenytoin, and primidone were selected for prediction analysis (Table 4, Fig. 2). The results have been generated using R statistics language (12). In particular, the functions and procedures from the

Table 2. Substitution rate of all identified substances according to ATC index with specified names and rates of substances from NO6, N05, N04, N03 and N02 groups.

No.	ATC index / Active substance for NO6, NO5, NO4, NO3, NO2	Substitution rate
1	C10	3.160.751
2	C09	1.885.997
3	A02	1.667.569
4	C08	1.352.818
5	C03	975.454
6	J01	875.929
7	A10	615.167
8	C07	383.991
9	N06	328.815
a	*Donepezilum*	53.905
b	*Fluoxetinum*	15.949
c	*Methylphenidatum*	41
d	*Mianserinum*	23.025
e	*Moclobemidum*	1.199
f	*Paroxetinum*	33.136
g	*Rivastigminum*	10.197
h	*Sertralinum*	57.774
i	*Tianeptinum*	13.895
j	*Venlafaxinum*	119.694
10	R03	299.264
11	G04	215.305
12	R06	176.680
13	M01	124.357
14	M05	123.608
15	C02	119.287
16	N05	107.768
a	*Amisulpridum*	3.281
b	*Aripiprazolum*	158
c	*Buspironum*	30
d	*Clozapinum*	308
e	*Diazepamum*	981
f	*Haloperidolum*	3.232
g	*Levomepromazinum*	174
h	*Olanzapinum*	32.536
i	*Perazinum*	22.357
j	*Quetiapinum*	27.189
k	*Risperidonum*	16.483
l	*Ziprasidonum*	1.039
17	J02	96.206
18	S01	91.640
19	N03	75.342
a	*Acidum valproicum*	7398
b	*Carbamazepinum*	14.480

Table 2. Continued.

No.	ATC index / Active substance for NO6, NO5, NO4, NO3, NO2	Substitution rate
c	*Gabapentinum*	3.991
d	*Lamotriginum*	24.655
e	*Levetiracetamum*	18.271
f	*Oxcarbazepinum*	1.538
g	*Phenobarbitalum*	168
h	*Phenytoinum*	18
i	*Primidone*	0
j	*Topiramatum*	4.823
20	N02	75.425
a	*Buprenorphinum*	62
b	*Fentanylum*	418
c	*Morphinum*	314
d	*Oxycodonum*	402
e	*Tramadolum*	33.541
f	*Tramadolum + Paracetamolum*	40.688
21	B01	65.747
22	L03	33.169
23	J05	21.701
24	N04	20.584
a	*Biperidenum*	7.155
b	*Bromocriptinum*	1.664
c	*Levodopum + Benserazidum*	3.756
d	*Levodopum + Carbidopum*	48
e	*Ropinirolum*	7.931
f	*Selegilinum*	31
25	M02	19.854
26	H03	15.317
27	G03	14.988
28	D01	14.395
29	L01	8.926
30	M04	8.495
31	L02	8.149
32	H02	6.448
33	A04	7.043
34	R01	6.542
35	C01	6.443
36	A07	6.269
37	L04	4.479
38	L09	3.786
39	A12	2.250
40	B03	1.526
41	P02	1.111
42	D07	823
Total		13.029.418

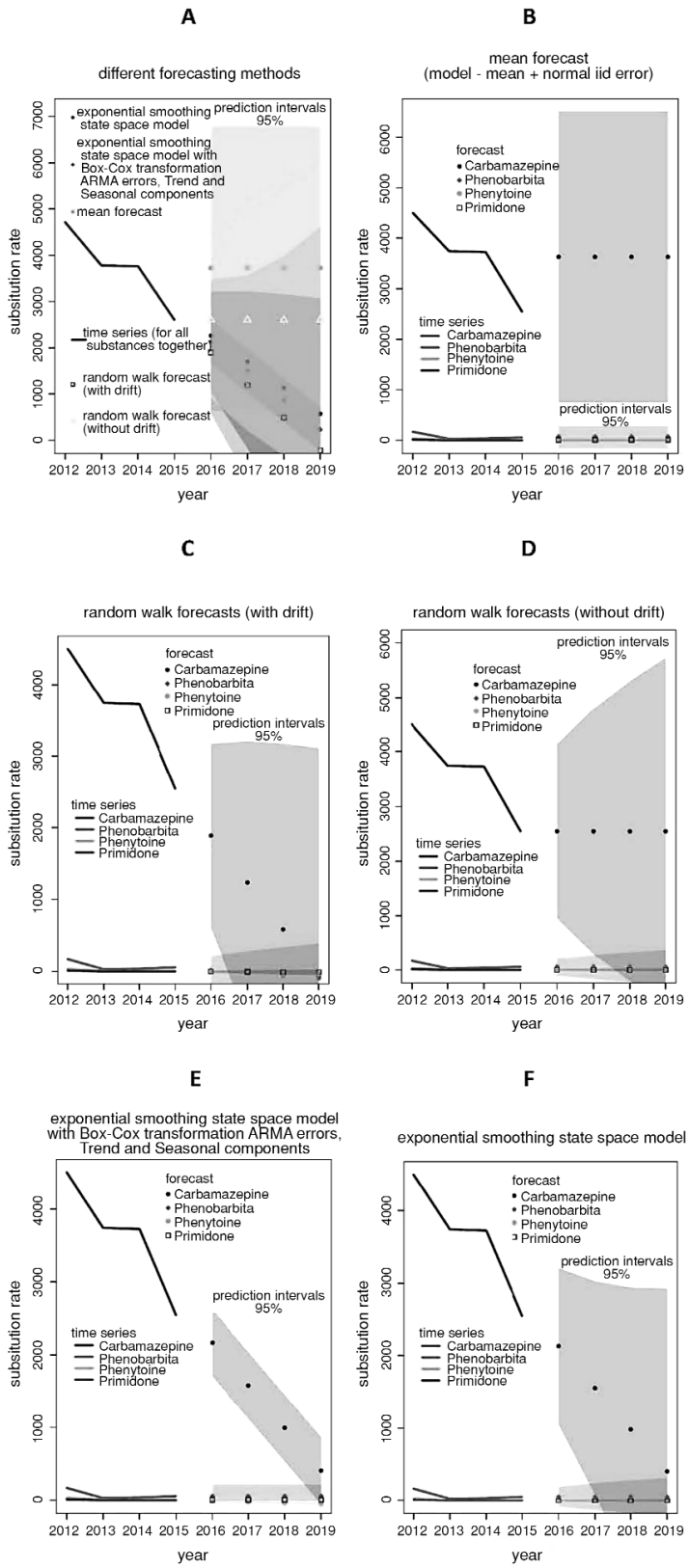
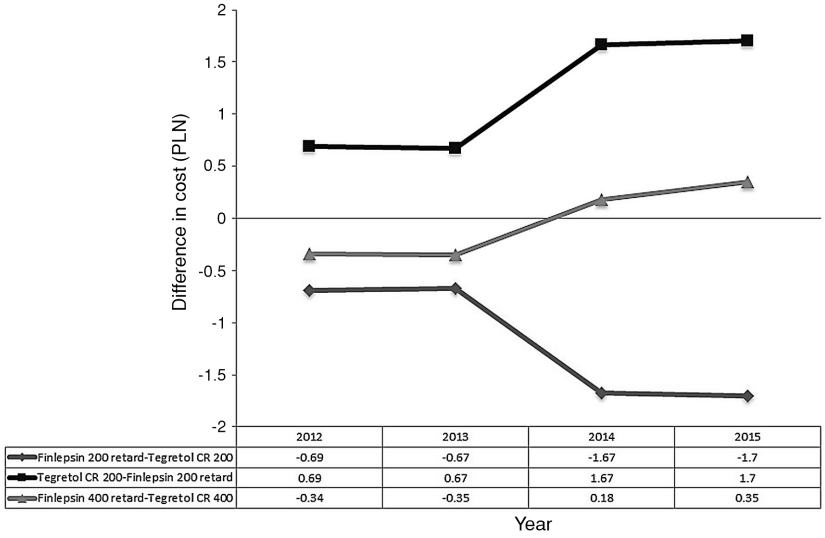


Figure 2. Prognosis of substitution rate for carbamazepine, phenobarbital, phenytoin, and primidone altogether; depending on the forecasting method (A); and separately in different forecasting methods (B, C, D, E, F)



	2012	2013	2014	2015
Finlepsin 200 retard-Tegretol CR 200	-0.69	-0.67	-1.67	-1.7
Tegretol CR 200-Finlepsin 200 retard	0.69	0.67	1.67	1.7
Finlepsin 400 retard-Tegretol CR 400	-0.34	-0.35	0.18	0.35

Figure 3. Differences in cost of substitution for the single substitution in three combinations in a four-year period

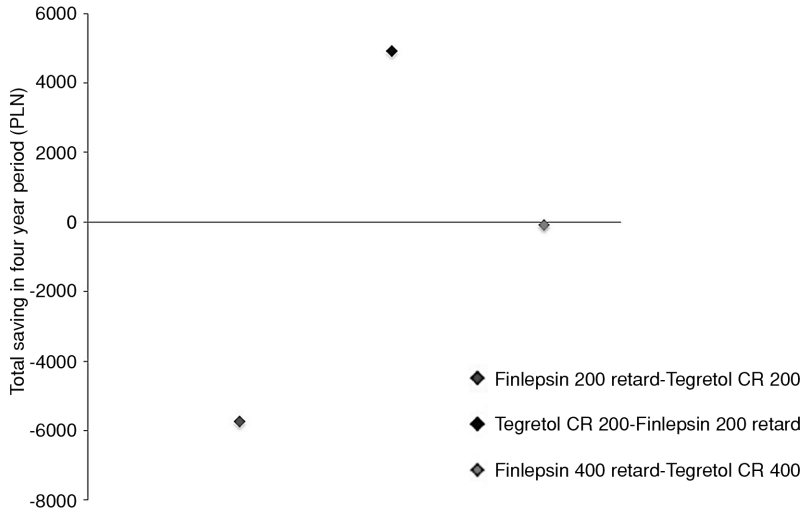


Figure 4. Total saving in cost of substitution for performed substitution in three combinations in a four-year period

forecast package have been used for a prediction of the variability of the number of exchanges over time. The software contains a lot of popular algorithms based on, among others, exponential smoothing or ARIMA models. The results, obtained by using the algorithms from the automatic time series forecasting, are presented in Figure 2.

Carbamazepine as most commonly used substance by Polish patients was classified for the analysis of cost saving reached at the moment of purchase. From 43 identified combinations of substituted (understood as a prescribed version of a drug-dispensed version of a drug) carbamazepine, those, which together filled over 50%, were selected for the detailed cost-saving check. The mean cost saving (from six reimbursement lists a year) at single purchase in approved combinations (3 types) is presented in Figure 3, while the mean total cost saving (a four-year) in identified population of approved combinations (3 types) is presented in Figure 4.

Section 2. Questionnaire-based

The observational study was conducted during June – July 2018 in the Department of Developmental Neurology of the Medical University of Gdansk by the medical doctors while collecting

medical history in the outpatient clinic as well as the hospital ward. The questionnaire contained questions as presented in Table 1.

Statistical analysis (Table 4) was performed in Statistica v13 (StatSoft, Tulsa, OK, USA) with the use of contingency tables comparing one variable (question) to the other, individually selected. Frequency distribution of the variables in this type of multivariate statistical analysis was carried out with the Pearson's chi-squared test and statistically significant p-value ($p < 0.05$).

RESULTS

The results of the current study are to evaluate the process of drug substitution in the most objective and wide-specific way. They are divided into those based on the retrospective data received from the NHF and those based on the questionnaire, which was distributed in the Department of Developmental Neurology of the Medical University of Gdansk and collected by the medical doctors of the clinic during medical history being collected in the outpatient clinic and hospital ward.

Starting from retrospective data based results; Table 2 presents the substitution rate of all identified substances according to ATC index with specified names (and their rates) of substances from ATC groups N02, N03, N04, N05, and N06. Neurological ATC groups represent 5% of total substitution rate, that is 607.935. The distribution of values of the variables for individual groups shows the boxplot (Fig. 1). The figure shows the first, the third quartiles, and median describing the number of exchanges in each group. The Kruskal-Wallis rank sum test has been used to check the statistical significance of the difference between the groups. The obtained result p-value = 0.1693 is not statistically significant

Table 3 determines the substitution rates of four substances: carbamazepine, phenobarbital, phenytoin, and primidone in a four-year period for each year, as well as in total. Figure 2 present the predictions of the substitution rates for all substances together and separately for each substance till the year 2019. Each colored area indicates the possible range of behavior of substitution rate for each model; symbols represent the mean values for each colored area.

Analysis of cost saving is presented in patients' perspective. In total, among approved for this purpose combinations (3 types) the substitution rate was at the level of 8393. Figure 3 determines differences in the cost of substitution for the single substitution in three combinations in a four-year period. Symbols on the figure (each year) represent the average in differences in cost of purchase from six reimbursement lists of each year. In Figure 4 the total saving in cost of substitution for performed substitution in three combinations in a four-year period; in the first case, the total saving is at the level of -5734.8 PLN; in the second case at the level of 4908.6 PLN; in the third case at the level of -99.2 PLN. Together the total saving is at the level of -925.4 PLN for 8393 drug substitutions.

The questionnaire base results start from Table 4, which present statistically significant responses and parameters (Pearson's chi-squared and p-value) of the questionnaire, together with the conclusion of each. The table presents only statistically significant question dependences.

Table 5 contains detailed affirmative responses (with %) of the questionnaire.

DISCUSSION

A review study from 2005, in which authors took under consideration 70 scientific articles to assess whether there are potential problems with the substitution of antiepileptic drugs (13, 14) highlights, that in major therapeutic areas disadvantages of the generic substitution are irrelevant or minor in comparison to the economic benefit. In epilepsy, a

Table 3. Substitution rate of identical INN name in a prescribed-dispensed form in following years.

Year	2012	2013	2014	2015	Total
INN name					
Carbamazepine	4.495	3.734	3.718	2.533	14.480
Phenobarbital	120	10	16	22	168
Phenytoin	16	2	0	0	18
Primidone	0	0	0	0	0
Total	4.631	3.746	3.734	2.555	14.666

Table 4. Statistically significant responses and parameters of the questionnaire.

No.	Questions	Responses (NO/YES) statistically significant	Statistical parameters
1.	1. Was the antiepileptic drug substituted in pharmacy (for containing the same INN and dose) since patients' last visit in doctors' office? 3. Did the patient observe/report changes in the efficacy of the undertaken therapy?	NO - 80 (78.43%) NO - 13 (12,75%)	N = 102, Pearson's chi-squared = 35.8944 p < 0.0001
2.	1. Was the antiepileptic drug substituted in pharmacy (for containing the same INN and dose) since patients' last visit in doctors' office? 4. Did the patient observe/report adverse reactions of the dispensed (substituted) drug?	NO - 80 (78.43%) NO - 15 (14.71%)	N = 102 Pearson's chi-squared = 27.3301 p < 0.0001
3.	1. Was the antiepileptic drug substituted in pharmacy (for containing the same INN and dose) since patients' last visit in doctors' office? 5. Did the patient observe/report discomfort in the usage of dispensed (substituted) drug?	NO - 80 (78.43%) NO - 20 (19.61%)	N = 102 Pearson's chi-squared = 7.4182 p = 0.0065
4.	1. Was the antiepileptic drug substituted in pharmacy (for containing the same INN and dose) since patients' last visit in doctors' office? 7. Are the decisions concerning substitution of antiepileptic drugs for Your patients consulted with You before they are made?	NO - 80 (78.43%) NO - 20 (19.61%)	N = 102 Pearson's chi-squared = 7.4182 p = 0.0065
5.	1. Was the antiepileptic drug substituted in pharmacy (for containing the same INN and dose) since patients' last visit in doctors' office? 8. Is the health condition of Your patients monitored after the substitution being made in pharmacy?	NO - 80 (78.43%) NO - 11 (10.78%) and YES - 11 (10.78%)	N = 102 Pearson's chi-squared = 44.8352 p < 0.0001

number of experts and professional bodies have recommended caution with generic substitution of drugs used in this condition.

Analysing data from the questionnaire presented in Table 4, if the antiepileptic drug was substituted in pharmacy patient did not observe/report changes in the efficacy of the undertaken therapy; did not observe/report adverse reactions of the dispensed (substituted) drug; did not observe/report discomfort in the usage of dispensed (substituted) drug; did not consult the decisions concerning substitution of antiepileptic drug with the medical doctor before they were made. If the antiepileptic drug was substituted in pharmacy the health condition of patients after the substitution is monitored in half of the raised answers. According to the collected answers, authors bring the conclusion that the collected data set is relatively small for rising high concerns; however, the data source is from the children's neurological ward; under 25 years old is expected to be the lowest age group undergoing drug substitution in general (10). Basing on detailed affirmative responses observed/reported changes included seizures increase, loss in efficacy, bad mood and behavioral disorders; observed/reported ADR included rash, behavioral disorders, nephrolithiasis, seizures increase, loss in efficacy, dizziness and headaches; whereas for discomfort: pills instead of syrup and worse taste of the syrup. It must be highlighted that there is currently no database, which could connect medical professions (prescribing – dispensing) in terms of factual data of substitution. It cannot be unequivocally claimed that decisions of substitution are therapeutic ones, because, according to the legal conditions, they take place in pharmacy beyond the medical doctor's knowledge (11).

Table 5. Detailed affirmative responses (with %) of the questionnaire.

For question 2: If yes, please fill in the trade name for the antiepileptic drug being used so far, and for the new antiepileptic, which was dispensed in pharmacy:		
Dependences (%) of individual substitutions among persons who raised affirmative answer; where name is a trade name of a pharmaceutical product.		
Name	Substitution rate	%
Trileptal® - Oxepilax®	3.00	13.64
Trileptal® - Karbagen®	1.00	4.55
Levetiracetam Teva® - Cezarius®	2.00	9.09
Lamitrin® - Lamotrix®	1.00	4.55
Lamitrin® - Symla®	1.00	4.55
Topamax® - Epitoram®	2.00	9.09
Oxepilax® - Karbagen®	1.00	4.55
Karbagen® - Neurotop®	1.00	4.55
Convival® - Convulex®	1.00	4.55
Keppra® - Levetiracetam Teva®	1.00	4.55
Keppra® - Cezarius®	2.00	9.09
Keppra® - Trund®	2.00	9.09
Trund® - Cezarius®	1.00	4.55
Trund® - Normeg®	1.00	4.55
Trund® - Levetiracetam Zorovit®	1.00	4.55
Tegretol® - Neurotop®	1.00	4.55
Total	22.00	100
For question 3: Did the patient observe/report changes in the efficacy of the undertaken therapy?		
Dependences (%) of observed/reported changes among persons who raised affirmative answer.		
Observed/reported change	Number	%
Seizures increase	4	40
Loss in efficacy	4	40
Bad mood	1	10
Behavioral disorders	1	10
Total	10	100
For question 4: Did the patient observe/report adverse reactions of the dispensed (substituted) drug?		
Dependences (%) of observed/reported ADRs among persons who raised affirmative answer.		
Observed/reported ADR	Number	%
Rash	1	12.5
Behavioral disorders	2	25
Nephrolithiasis	1	12.5
Seizures increase	2	25
Loss in efficacy	1	12.5
Dizziness and headaches	1	12.5
Total	8	100
For question 5: Did the patient observe/report discomfort in the usage of dispensed (substituted) drug?		
Dependences (%) of discomfort among persons who raised affirmative answer.		
Discomfort	Number	%
Pills instead of syrup	1	50
Worse taste of the syrup	1	50
Total	2	100

One of the most important issues (after safety of a patient) to concern in terms of generic substitution is: economic value and legal situation, understood as potential savings vs. potential costs and legal implications considering practical aspects of drugs being used in certain conditions; in example differently for insulin products (biological medicines), and differently for medicines used in epilepsy (in example NTI medicine).

Looking at Figure 2 it is noticeable that regardless of the method being used, the substitution rate predicts to decrease or remain constant in the future. According to the authors, it is a good trend from one hand: there is no regulation and guidelines standardizing substitution in use in Poland. On the other hand, substitution is to, a priori, to bring savings. For example in the US more than one-third of total savings (in 2012) arising from drug substitution came from central nervous system drugs: $75 billion (15). Looking at Figures 3 and 4 it is noticeable that the total saving arising from the performed substitution of carbamazepine medications from the patients' perspective is not enormous. The maximum difference in cost in substitution at the pharmacy was identified around the level of 1.7 PLN, and maximum extra pay at the same level. Together the total saving is at the level of -925.4 PLN for 8393 drug substitutions of active substance carbamazepine in a 4-year period in five voivodeships. In Figure 1, the Kruskal-Wallis rank sum test shows that there is no difference in values between the substitution in specified neurological groups in this case. Authors here, once more highlight, that substitution was hand over to the market rules and is driven by the accessibility of the drugs in the pharmacies inventories (11).

Pharmacists have legal responsibilities and are accountable for their acts or omissions while practicing their profession. Standards of practice for pharmacies are established to ensure professional skills and knowledge are on a par with scientific specialists in their area of practice to ensure the greatest benefit to the patient. In Poland, there are no standardized Good Pharmacy Practice guidelines in use. This means that Polish pharmacists are only guided by their statutory (legal) obligations and by ethical rules, and not by practical standards. This situation contrasts with that of pharmacists in many other European countries. For example, Dutch pharmacists have a "Guideline for generic substitution" which was established by the Royal Dutch Pharmacists Association. In those guidelines is states that medical products with a narrow therapeutic index e.g., traditional anti-epileptic drugs (phenobarbital and other barbiturates, carbamazepine, ethosuximide, phenytoin, oxcarbazepine, sulthiame, trimethadione, valproic acid) are subject to stricter bioequivalence requirements than other medications and their interchangeability is questioned (16).

CONCLUSIONS

Consent for automatic pharmacy substitution, on the example of NTI products used in epilepsy, bequeath a doubt about the benefits and costs (in ex. further visits at the physician's office) of this process as well as the integrity of health care system in Poland. Further studied need to be performed in order to carefully evaluate all the costs that are the consequence of substitution at the end and how adults react at the act of substitution, since a number of experts and professional bodies have recommended caution with generic substitution of drugs used in epilepsy.

This study shows, that substitution in epilepsy in Polish background exists and, in terms of most often substituted epileptic drug (carbamazepine), there is no saving for patients in total but extra pay at the level of 925,4 PLN. The study highlights the necessity of planning process and evaluation of current market regulations between subjects in the creation of rational and effective regulation as in other countries special categories for drug substitution exists.

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