

Methodology of demand study for proton pump inhibitors drugs

O. Balicka¹, T. Germanyuk¹, O. Kryvoviaz¹, T. Ivko¹, O. Toziuk¹, O. Bobrowska¹, V. Koval¹, M. Artemchuk¹, U. Grygoruk¹, S. Kryvoviaz²

¹Department of Pharmacy, Candidate of Pharmaceutical Sciences, Docent, National Pyrogov Memorial Medical University, Vinnytsia, Ukraine, ²Department of Eye Diseases, Candidate of Medical Sciences, Docent, National Pyrogov Memorial Medical University, Vinnytsia, Ukraine

Abstract

Aim: This study aims to describe the method and practical application of flexible tools for development of non-standard designs of selection models, implemented in the SAS system. The main research task was to study the demand for proton-pump inhibitors drugs (PPIs) that are prescribed for the treatment of gastric ulcer and duodenal ulcer. The difficulty was in the a priori present dependence on the choice of alternative on the attributes of other alternatives in the choice set. the dependence of choosing an alternative from the presence of others in the selection network is also non-standard. Hence, if the desired drug is absent in the pharmacy chain, the patient must choose the next desired one from the available ones. All this requires non-standard approaches in the creation of design, and therefore, of the corresponding tools. **Materials and Methods:** LIMDEP/NLOGIT and Sawtooth software; toolbox SAS. **Results and Discussion:** There are five groups of PPI according to the active ingredient: Omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole medications. Taking into account the possibility of quadratic effects of the price for the drug at the patient's discretion, we have used three-level attributes of the price, which provide the assessment of both linear and quadratic price effects. In the capacity of the effectiveness of the selected treatment regimens of gastric disease, we have chosen the anatomical cicatrization of mucosa damage at week 4 of treatment, according to the published specialized researches. **Conclusion:** Increasing of the analytical capabilities of the choice modeling allows using more flexible designs.

Key words: Duodenal ulcer, gastric ulcer, proton-pump inhibitors drugs, toolbox SAS

INTRODUCTION

As the market of medical services is growing in Ukraine, modeling of the patient's choice plays a crucial role. However, the researcher himself faces a difficult choice of tools for creation of design and data analysis. The main software is the specialized ones: Packages bayesm, mlogitR (<https://www.r-project.org/4>), Sawtooth (<http://www.sawtoothsoftware.com/>), StatWizards (<http://www.statwizards.com/>), ChoiceModelR™ (<https://www.decisionanalyst.com/download/>), Biogeme (<http://transp-or.epfl.ch/>), LIMDEP/NLOGIT (<http://www.limdep.com/>), package DCM (<http://www.econ.cam.ac.uk/DCM/DCMWebPage.htm>), Lenk's Code (<http://webuser.bus.umich.edu/plenk/index.htm>), and Kenneth Train's Matlab Code (<http://eml.berkeley.edu/~train/>).

However, considering all the above-mentioned software, the possibilities of design development are provided only in LIMDEP/NLOGIT and Sawtooth software. Comparison of the main features of these softwares with SAS determined the use of the latter.

MATERIALS AND METHODS

- LIMDEP/NLOGIT and Sawtooth software;
- Toolbox SAS;
- Proton-pump inhibitors (PPIs) drugs.

Address for correspondence:

O. P. Balicka, Department of Docent of Pharmacy, Candidate of Pharmaceutical Sciences, National Pirogov Memorial Medical University, Ukraine.
E-mail: Olesyabal1984@gmail.com

Received: 13-02-2018

Revised: 02-03-2018

Accepted: 13-03-2018

RESULTS AND DISCUSSION

Description of Alternatives

There are five groups of PPI according to the active ingredient: Omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole medications.^[1]

We have been guided by the following generally accepted principles when including drugs into the research:

1. Prevalence of the medication on the pharmaceutical market
2. Prevalence of the medication on doctor's orders
3. Availability of reliable data, based on randomized clinical studies, relating to efficiency.

Having been guided by these principles, we focused on the medications of three active ingredients, namely: Rabeprazole, pantoprazole, and esomeprazole. The omeprazole medications are not included because of the proven higher efficiency of esomeprazole medications.^[2,3] Lansoprazole medications are not included because of the proven short acid-inhibitory effects.^[4,5] In addition, the brand of the drugs is absent on the pharmaceutical market. In the research rabeprazole, medications are represented by Pariet (brand), as well as by the effective generic Barol. Rabemac has a reliable clinically lower effect and prescribed by doctors rarely, that is, why it is not included in the research. Pantoprazole medications are represented by Controloc (brand), as well as by generics Pulcet and Nolpaza. Pantosan effect is not significantly different from the effects of Pulset and Nolpaza, though it is much more expensive, that is, why Pantosan is not included in the research. We could not find a sufficient evidential base regarding a newer drug - Ulsepan, that is, why we did not examine this medication either. Esomeprazole medications are represented by a brand-name product Nexium and generic Ezolong.

In the description of alternatives, the following attributes are included price, clinical efficiency, and the probability of side effects, who it is prescribed by. The last attribute is our innovation for pharmacoeconomic and marketing analyses. The study of the efficiency of prescriptions in further analysis, as well as understanding of patient's credibility to doctor's prescriptions in the demand analysis and, correspondingly, the possibilities of physician-induced demand became the basis for its introduction.

Taking into account the possibility of quadratic effects of the price for the drug at the patient's discretion, we have used three-level attributes of the price, which provide the assessment of both linear and quadratic price effects.^[6-8] To determine the levels of the price attributes of design, we have used a statistical approach based on the variation coefficient. We have chosen a low variation, namely, 10% of the average value. Thus, the minimum level of price

attribute makes up the average level of the index - 10% of the average (typical) level. The average level matches the typical level. The maximum level of the price attribute makes up the average level of index + 10% of its typical level.

In the capacity of the effectiveness of the selected treatment regimens of gastric disease, we have chosen the anatomical cicatrization of mucosa damage at week 4 of treatment, according to the published specialized researchers. The basic principles that we were guided by in choosing the researches were: (1) The plan of the controlled randomized study, (2) the preference has been given to domestic studies, as the methods of their implementation, and most importantly, patients and doctors populations, the specific features of clinical case management are a priori disparate with the foreign ones. Since we have been interested only in linear effect, we have restricted ourselves to two gradations - $10\% \pm$ of average efficiency.

Two gradations of attribute of side effects probability, which we have taken the same for all seven alternatives, have been similarly identified.

Seven alternatives, attributes, and their gradations are set forth in Table 1.

Design specific features. The design is asymmetrical, brand new (brands are created by PPI drugs, which determine alternatives), with the possible absence of certain alternatives. The lack of alternatives is marked by additional gradation of price attribute.

Determination of Acceptable Design Size

Using the linear model (LM) design for X1-H28, the total number of parameters, including the constant, all the main effects (of the first order) and the effects of the second order, make up 57 (7 main drug effects + constant (1) + number of independent parameters of prices ($21=[4-1]*7$) + number of independent parameters of the drug effects ($7=7*[2-1]$) + number of independent parameters of the drug side effects ($7=7*[2-1]$) + number of independent parameters of interactions of drug type and variant of prescription ($14=[3-1]*7$). The number of parameters is calculated for the coding of price as a categorical variable. The actual number of parameters in the non-LM of choice (MC) is higher at 84 by means of inclusion of cross-effects (CEs), price * alternative ($42=7*[7-1]$) and CEs of the drug availability (AE), drug availability * alternative ($4=7*[7-1]$). Thus, the sum of the parameters of the MC makes up 141. Therefore, the number of independent bands of LM design should exceed 57 (independent number of the LM parameters), and the MC design - 141.

Table 1: The general scheme of study design attributes on circulated treatment regimens of gastric ulcer and duodenal ulcer

Alternative	Attribute	Levels	Medication	Description
1.	X1	4	Pariet	Price: 760/840/920/unavailable
2.	X2	4	Barol	Price: 100/110/120/unavailable
3.	X3	4	Controloc	Price: 370/410/450/unavailable
4.	X4	4	Pulset	Price: 290/320/350/unavailable
5.	X5	4	Nolpaza	Price: 180/200/220/unavailable
6.	X6	4	Nexium	Price: 540/600/660/unavailable
7.	X7	4	Ezolong	Price: 160/180/200/unavailable
1.	X8	3	Pariet	Drug, wich designed of gastroenterologist/other physician specialty/without appointment
2.	X9	3	Barol	Designed: -/-/-
3.	X10	3	Controloc	Designed: -/-/-
4.	X11	3	Pulset	Designed: -/-/-
5.	X12	3	Nolpaza	Designed: -/-/-
6.	X13	3	Nexium	Designed: -/-/-
7.	X14	3	Ezolong	Designed: -/-/-
1.	X15	2	Pariet	Effect: 60/80
2.	X16	2	Barol	Effect: 80/100
3.	X17	2	Controloc	Effect: 70/90
4.	X18	2	Pulset	Effect: 80/100
5.	X19	2	Nolpaza	Effect: 60/80
6.	X20	2	Nexium	Effect: 80/100
7.	X21	2	Ezolong	Effect: 80/100
1.	X22	2	Pariet	Side effect: 10/30
2.	X23	2	Barol	Side effect: 10/30
3.	X24	2	Controloc	Side effect: 10/30
4.	X25	2	Pulset	Side effect: 10/30
5.	X26	2	Nolpaza	Side effect: 10/30
6.	X27	2	Nexium	Side effect: 10/30
7.	X28	2	Ezolong	Side effect: 10/30

To find the number of bands of LM design that will ensure the compromise level of the design efficiency, orthogonality, and balance, we have used a macro% MktRuns:

%MktRuns (4**73**72**14, interact = $\times 1^* \times 8 \times 2^* \times 9 \times 3^* \times 10 \times 4^* \times 11 \times 5^* \times 12 \times 6^* \times 13 \times 7^* \times 14$)

The analysis of listing variants [Table 2] shows two convenient sizes according to the criteria of number of violations of the orthogonality of effects assessments and balance (estimated number of dividers, formed by various combinations of the number of factors gradation). The design with 96 bands is considered as minimal for size, which is not only provided by dividers 9 and 36. However, among our factors, there is no combination of factors, the gradation product of which gives 9 or 36. That is, this design can evaluate all main effects and

the effects of the second order. At conversion into MC design with sets sized 3, the capability of assessment $192=96*(3-1)$ of independent parameters that significantly exceeds 141 is provided.

Another size, worthy of attention, is the size of 144 bands, which on the whole has no violations of the orthogonality and problems of balance, and, of course, has a higher efficiency than the previous one [Table 2].

CONCLUSIONS

Increasing of the analytical capabilities of the choice modeling allows using more flexible designs. However, only a few specialized soft commodities allow doing it. We have conducted

Table 2: Possible sizes of the design for criteria of the number of violations of the orthogonality and problems of balance

Possible sizes of the design	Failure	Missing dividers
144*	0	
72	21	16
96	21	9
192	21	9
216	21	16
240	21	9
120	42	9 16
168	42	9 16
108	119	8 16
180	119	8 16
50 S	392	3 4 6 8 9 12 16

*100% effective design. Full factor design=587,068,342,272.

S: Saturated design. Least possible design for the study goals. Inability means the quantity of effects 3rd and higher order that design is not able to estimate

a study of the main characteristics of the last ones and have chosen the toolbox SAS, which is diversified and flexible. At creating design of the selection model for studying the demand for IPP drugs, we had difficulties, particularly as for a priori present dependence on choice of alternative on the attributes of other alternatives in the set of choice. The dependence on choosing an alternative on the presence of the other ones in the set was also an unusual moment. Despite these complications, the MC design with good properties in the traditional plane of orthogonality, balance, and efficiency has been received.

REFERENCES

1. Mashkovskiy MD. Pharmaceuticals Tools. 16th ed. Kharkov: Torsing; 1998.
2. Yastrebkova LA. Comparative Clinical Efficiency and Safety of Rabeprazole (Pariet) and Esomeprazole (Neksyum)-Acid Diseases of Gastrointestinal Tract//MEDGAZETA. 08.07.2009.
3. Abdulhanyeva DI, Prokhorov YF, Sadykov EF. Efficiency of pariet in therapy of Acid diseases of upper sections of gastrointestinal tract//materials of 11 Russian gastroenterological week. Russ Mag Gastroenterol 2005;5:18-22.
4. Avdoshina SP, Favstova SK, Pimenov NV. Modern technology in gastroesophageal reflux disease therapy in children with the disease allergy//materials of 10 Russian gastroenterological week. Russ Mag Gastroenterol 2004;5:108-11.
5. Alekseeva OP, Kurisheva MA. Algorithm of diagnosis and of treatment of gastroesophageal reflux disease in patients with asthma//materials of 9 Russian gastroenterological week. Russ Mag Gastroenterol 2003;5:5-8.
6. Kuhfeld WF. Dierence schemes via computerized searches. J Stat Plan Inference 2005;127:1-2, 341-6.
7. Sawtooth Software. The MaxDi/Webv6.0 Technical Paper; 2007. Available from: <http://www.sawtoothsoftware.com>.
8. Suen CY, Kuhfeld WF. On the construction of mixed orthogonal arrays of strength two. J Stat Plan Inference 2005;133:555-60.

Source of Support: Nil. **Conflict of Interest:** None declared.