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Wykorzystanie danych z praktyki klinicznej (ang. Real-World Evidence, RWE) w optymalizacji farmakoterapii w wybranych jednostkach chorobowych

Utilization of Real-World Evidence (RWE) in pharmacotherapy optimization in selected therapy areas

Rozprawa doktorska na stopień doktora
w dziedzinie nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki o zdrowiu
przedkładana Radzie Dyscypliny Nauk o Zdrowiu
Warszawskiego Uniwersytetu Medycznego

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Key words: real-world evidence, RWE, pharmacotherapy optimization, health policy, societal perspective, outcomes research, health economics

List of publications constituting this doctoral thesis

This dissertation consists of four thematically related research articles with a combined IF score of 9,325 and 285 MEiN points.

[1] **Krupa, D.**, Czech, M., Chudzyńska, E., Koń, B., & Kostera-Pruszczyk, A. (2023). Real World Evidence on the Effectiveness of Nusinersen within the National Program to Treat Spinal Muscular Atrophy in Poland. Healthcare (T. 11, Issue 10, s. 1515). MDPI AG. https://doi.org/10.3390/healthcare11101515

Ministry of Science points 40
Impact Factor 2.800

[2] **Krupa, D.**, Czech, M., Pinkas, J., & Mosiołek, A. (2022). Impact of COVID-19 Pandemic on the Use of Antidepressant and Antianxiety Pharmaceuticals as Well as Sick Leave in Poland. International Journal of Environmental Research and Public Health (T. 19, Issue 4, s. 2135). MDPI AG. https://doi.org/10.3390/ijerph19042135

Ministry of Science points 140

[3] Kardas, P., Lichwierowicz, A., Urbański, F., Szadkowska-Opasiak, B., Karasiewicz, E., Lewek, P., **Krupa, D.**, & Czech, M. (2021). The Potential to Reduce Patient Co-Payment and the Public Payer Spending in Poland through an Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by the Real-World Big Data Analysis. Pharmaceutics (T. 13, Issue 8, s. 1165). MDPI AG. https://doi.org/10.3390/pharmaceutics13081165

Ministry of Science points 100
Impact Factor 6.525

[4] Czech, M., Jasinski, Z. & **Krupa, D.** (2015). Real-life treatment patterns and medication costs in patients with hypertension treated with ramipril monotherapy or ramipril loose and fixed combinations in Poland. Journal of Health Policy & Outcomes Research (Issue 2, s. 31–44). Fundacja Pro Medicina. https://doi.org/10.7365/jhpor.2015.2.4

Ministry of Science points 5

Additional publications in peer reviewed journals on topics related to public health not included in the doctoral thesis:

[1] Ishida, M., Kuroiwa, Y., Yoshida, E., Sato, M., **Krupa, D.**, Henry, N., Ikeda, K., & Kaneko, Y. (2018). Residual symptoms and disease burden among patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. W Modern Rheumatology (T. 28, Issue 5, s. 789–799). Oxford University Press (OUP).
https://doi.org/10.1080/14397595.2017.1416940

Ministry of Science points 20
Impact Factor 1.973

Additional indexed publications on topics related to public health:

[1] Czech, M., Gierczyński, J., Jakubiak, K., **Krupa, D.**, Rejdak, K., & Władysiuk, M. (2021). Rozwój terapii lekowych w leczeniu chorób neurologicznych. Development of drug therapies in the treatment of neurological diseases. Available online: https://doi.org/10.13140/RG.2.2.10766.89928
ISBN: 978-83-958398-2-5
Chapter 4 Socio-economic consequences of neurological diseases

[2] Jakubiak, K., Czech, M., Gierczyński, J., **Krupa, D.**, & Władysiuk, M. (2020). Rozwój terapii lekowych w leczeniu chorych na nowotwory. Nowości. Innowacje. Przełomy. Development of drug therapies in the treatment of cancer patients. News. Innovations. Breakthroughs. Available online: https://doi.org/10.13140/RG.2.2.29291.77603
ISBN: 978-83-958398-0-1
Chapter 1 Global impact of oncological diseases
Chapter 4 Impact of COVID-19 pandemic on the situation in oncology

[3] Jakubiak, K., Obarska, I., Czech, M., **Krupa, D.**, Stajszczyk, M., Owczarek, W., Jarosław Kierkuś, Jurczak, W., & Gierczyński, J. (2019). Access to biological treatment in Poland. Dostęp do leczenia biologicznego w Polsce. Available online: https://doi.org/10.13140/RG.2.2.35517.00483
Chapter 2 – A literature review on the replacement of biological drugs by biologically equivalent drugs (biosimilars) in clinical practice

Table of Contents

1. List of abbreviations

AOTMiT	– (pol. Agencja Oceny Technologii Medycznych i Taryfikacji) Agency for Health Technology Assessment and Tariff System
EMA	– European Medicines Agency
EMR	– Electronic Medical Records
FDA	– US Food and Drug Administration
FDC	– Fixed dose combination
GDP	– Gross Domestic Product
HCP	– Healthcare professional
MoH	– Ministry of Health
NICE	– National Institute for Care Excellence
NFZ	– (pol. Narodowy Fundusz Zdrowia) National Health Fund in Poland
OECD	– Organization for Economic Co-operation and Development
OTC	– Over the counter
PLN	– Polish zloty
RCT	– Randomized Clinical Trials
RWD	– Real-World Data
RWE	– Real-World Evidence
Rx	– Prescription medication
SMA	– Spinal muscular atrophy
ZUS	– (pol. Zakład Ubezpieczeń Społecznych) Social Insurance Instutition in Poland

2. Summary of the dissertation in Polish

Dowody oparte o dane z praktyki klinicznej (RWE) to prężnie rozwijająca się dziedzina nauk o zdrowiu publicznym, ponieważ oferują niespotykane dotąd bogactwo opisu stanu zdrowia populacji i ich walki z różnymi chorobami. Na całym świecie popularność RWE wzrasta, choć ich całkowity potencjał zdecydowanie przewyższa ich aktualne wykorzystanie. W dalszym ciągu dowody z praktyki klinicznej są stosowane relatywnie wąsko, a ich największa popularność często ogranicza się do rejestracji produktów farmaceutycznych lub decyzji refundacyjnych. Jednocześnie kluczowy obszar ich faktycznego wpływu na wyniki zdrowotne i zachowania pacjentów jest zbyt rzadko mierzony, analizowany i wykorzystywany w procesach decyzyjnych. Szersze użycie RWE, m.in. w optymalizacji farmakoterapii w warunkach praktyki klinicznej zapewnia bardziej całościowe i praktyczne zrozumienie wyników leczenia, kosztów i implikacji w świecie rzeczywistym, dostarczając cennych spostrzeżeń do podejmowania decyzji w oparciu o dowody i opracowywania polityki w warunkach systemu opieki zdrowotnej.

Niniejsza rozprawa doktorska przedstawia wybrane aspekty wykorzystania danych RWE w kontekście społecznych implikacji farmakoterapii w Polsce, podkreślając równocześnie jej potencjał jako kluczowego narzędzia dla planistów polityki zdrowotnej. W rozprawie zwrócono uwagę na wieloaspektowy wpływ farmakoterapii, wykraczający poza opiekę zdrowotną, a rozciągający się na takie obszary jak dobro pacjenta, produktywność pracowników i zrównoważony rozwój gospodarczy. Kluczową kwestią poruszoną w rozprawie jest znaczenie wykorzystania dostępnych źródeł danych do skutecznego planowania, monitorowania i oceny wyników interwencji farmakologicznych w celu optymalizacji alokacji zasobów i uzyskania maksymalnych korzyści z jej stosowania.

Rozprawa składa się z czterech powiązanych tematycznie artykułów naukowych opublikowanych w recenzowanych czasopismach. W artykule 1 przedstawiono kwestię choroby rzadkiej, badając jej wpływ na pacjentów, opiekunów, placówki opieki zdrowotnej i system finansowania publicznego. Na podstawie studium przypadku rdzeniowego zaniku mięśni (ang. *spinal muscular atrophy*, SMA) w artykule opisano efekty wdrożenia programu opieki nad pacjentami, który wpłynął na uzyskanie poprawy wyników klinicznych pacjentów przy jednoczesnym utrzymaniu całkowitych kosztów na przewidywalnym poziomie. Zostało to osiągnięte również poprzez inicjatywy takie jak program badań przesiewowych noworodków, czyli położenie nacisku na proaktywne podejście do opieki zdrowotnej. W artykule 2 zbadano związek między konsumpcją środków farmaceutycznych a produktywnością pracowników, szczególnie w kontekście pandemii Covid-19.

Podkreśla on rozbieżność, w przypadku której pomimo znaczących zmian w zachowaniach pracowników spowodowanych pandemią, wykorzystanie leków nie zmieniło się w znaczący sposób. Eksponuje to problem polityki zdrowia psychicznego i sugeruje potrzebę dalszych badań i działań politycznych w celu zaadresowania potrzeb pacjentów w tym aspekcie. W artykule 3 omówiono potencjalne korzyści z substytucji leków generycznych jako narzędzia polityki wywierającego pozytywny wpływ na pacjentów i płatnika. Podobnie Artykuł 4 ukazuje wyższość terapii skojarzonej pod względem kosztów i przestrzegania zaleceń przez pacjenta w porównaniu z podejściami alternatywnymi.

Praca jest zwieńczona praktycznymi implikacjami, opowiadając się za wykorzystaniem danych do optymalizacji farmakoterapii w celu osiągnięcia korzyści społecznych, takich jak zmniejszenie kosztów dla pacjentów i płatnika publicznego, poprawa wyników zdrowotnych, lepsze stosowanie się do zaleceń lekarskich i zwiększona produktywność pracowników. Kluczowe rekomendacje obejmują większe wykorzystanie RWE w kształtowaniu polityki zdrowotnej i optymalizacji farmakoterapii, zwiększanie dostępu do opieki i diagnostyki, promowanie optymalnego wyboru terapii i jej przestrzegania, zwiększanie świadomości na temat korzyści płynących z farmakoterapii oraz inwestowanie w inicjatywy takie jak badania przesiewowe noworodków pod kątem chorób rzadkich.

Podsumowując, praca ta podkreśla znaczenie optymalnej farmakoterapii w kształtowaniu polityki zdrowotnej i oferuje wgląd w to, w jaki sposób można wykorzystać dane, aby stawić czoła wyzwaniom społecznym i poprawić efektywność opieki zdrowotnej w Polsce.

3. Summary of the dissertation in English

Real-World evidence (RWE) is a dynamically developing field in public health science, as it offers previously unprecedented richness in describing the health status of populations and their struggle with various diseases. Despite the rise in the use of RWE worldwide, its full potential is yet to be realized. RWE continues to be formally used in a relatively narrow way, and its popularity is often limited to registration of pharmaceuticals or reimbursement decisions. At the same time, the key element of the actual impact on patients' outcomes and behaviors is at the moment rarely measured, analyzed and utilized in decision making in healthcare. Hence, further use of RWE in optimizing pharmacotherapy offers a more holistic and practical understanding of treatment outcomes, costs, and real-world implications, providing valuable insights for evidence-based decision-making and policy development in healthcare systems.

This doctoral thesis presents the selected aspects of RWE utilization in the context of the societal implications of pharmacotherapy in Poland, emphasizing its potential as a crucial tool for health policy planners. The dissertation highlights the multifaceted impact of pharmacotherapy beyond healthcare, extending to areas such as patient wellbeing, worker productivity, and economic sustainability. It emphasizes the importance of utilizing available data sources to effectively plan, monitor, and assess the outcomes of pharmacologic interventions to optimize resource allocation for the purpose of achieving maximum available societal benefits.

The thesis consists of four thematically linked scientific articles published in peer reviewed journals. In Article 1, the focus is on the management of rare diseases, examining its impact on patients, caregivers, healthcare facilities, and the public financing system. Through the case study of spinal muscular atrophy (SMA), the article demonstrates the feasibility of implementing a system that improves patient outcomes while maintaining costs within a manageable budget. This was feasible also by the introduction of initiatives like the newborn screening program, which emphasizes a proactive approach to healthcare. Article 2 explores the link between pharmaceutical consumption and worker productivity, particularly in the context of the COVID-19 pandemic. It highlights a discrepancy where despite significant changes in worker behavior due to the pandemic, pharmaceutical consumption remained unaffected. This underscores an issue in mental health policy, suggesting a need for further investigation and policy action to address underlying issues. Article 3 discusses the potential benefits of enforced generic substitution as a policy tool to positively impact patients and the public payer. Similarly, Article 4 demonstrates the superiority of combination therapy in terms of cost and patient adherence compared to alternative approaches.

The thesis concludes with practical implications, advocating for the use of pharmacotherapy to achieve various societal benefits such as reduced costs for patients and public payers, improved healthcare outcomes, enhanced treatment adherence, and increased worker productivity. Key recommendations include stronger utilization of RWE in shaping health policy and optimizing pharmacotherapy, widening of access to care and diagnosis, promoting optimal therapy selection and adherence, increasing awareness of the benefits of pharmacotherapy, and investing in initiatives such as newborn screening for rare diseases.

Overall, this work underscores the importance of optimal pharmacotherapy in shaping health policy and offers insights into how data can be leveraged to address societal challenges and improve healthcare outcomes in Poland.

4. Introduction

4.1 Health status of the Polish population

Despite significant advancement that Poland has made even over the last 10 years, the health status of the population is poorer than in case of other European countries [1]. Life expectancy at birth in Poland is estimated to be at 77,4 years for both sexes in 2022. In Czech Republic it is 79,1 years, in Germany 80,7 years, in Sweden 83,1, in Spain 83,2 years.

The OECD and Eurostat have developed additional measures to capture and compare the health status between countries. The organizations define:

- preventable mortality – deaths before the age of 75 that could have been avoided through effective public health and primary prevention interventions (to reduce incidence of disease)
- treatable mortality – deaths before the age of 75 that could have been avoided through timely and effective health care interventions, including secondary prevention and treatment;

In terms of treatable mortality, an estimated 117 deaths per 110 000 population in Poland in 2020 could have been avoided by improved healthcare interventions. In comparison, the same indicator in the same period for Czechia was 99, in Germany 66 and in Spain 51.

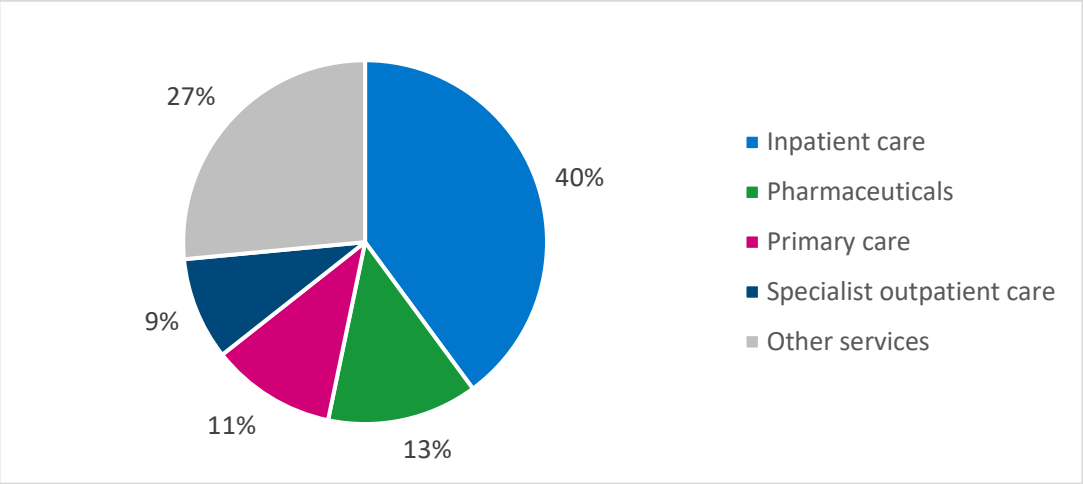
The presented data reinforce the need for improvements in accessibility and quality of healthcare interventions in Poland.

4.2 Healthcare spending in Poland

The costs of healthcare have been **growing** on a continuous basis over the last years. According to data from OECD, the per capita spending for healthcare in Poland increased from 3 032 PLN in 2015 to 5 459 PLN in 2022 [2], the most recent available data. The resulting annual growth is 8.8%. Comparatively, real GDP in the same period grew at an average rate of 4.1% per year [3]. The figures indicate that the issue of healthcare expenditures' dynamic in the economy requires remediation.

Within the healthcare budget of the National Health Fund (NFZ, pol. Narodowy Fundusz Zdrowia) for 2024, expenditures on drugs are the second largest category, after inpatient care in a hospital setting. Out of the total budget of 157.6 billion PLN, 21.1 billion PLN was devoted to pharmaceuticals (including community pharmacy reimbursement, drug programs and chemotherapy) [4].

Figure 1 Split of the 2024 healthcare budget of the NFZ in Poland



Source: Own analysis based on NFZ data [4]

4.3 Role of pharmacotherapy optimization in the healthcare system

Proper application of pharmacotherapy is associated with improved health state, chronic disease management, alleviation of negative symptoms, shortened inpatient stays, diminished requirement for other healthcare services. Improper pharmacotherapy or lack thereof will lead to worsening of the situation in all of the mentioned aspects [5, 6]. This in turn leads to increased healthcare costs across multiple budget categories presented above. Moreover, the impact of foregone medical benefits related to lack of appropriate pharmacotherapy will extend beyond healthcare, exerting negative externalities on the patients and their families, worker productivity and the economy [7]. The field of pharmacoeconomic science deals with the issue of measurement of direct and indirect costs [8] of healthcare interventions, and the impact of those on budgets [9]. Therefore, it can be considered best practice to look to pharmacoeconomic evaluations to answer the question on how to efficiently spend money on healthcare.

4.4 Real-World Evidence (RWE) as a resource for knowledge on measuring healthcare interventions

Real-World Evidence is an umbrella term that refers to insights relating to patient health status and/or delivery of health care that is collected with some regularity from a myriad of sources [10]. RWE arises from the analysis of the so-called Real-World Data (RWD). This data could take the form of

[11]: electronic medical records (EMR), patient registries, medical or insurance claims data, digital health technologies, like wearable devices or apps, and others. Alternatively, it can be defined as data on topics related to health of an individual or group of individuals that do not come from rigorously controlled clinical trials but instead were generated in everyday setting.

The popularity of RWE has been increasing dynamically over the past years, for several reasons: It offers information previously unavailable to decision makers, it reduces the impact of some of the potential bias caused by meticulous recruitment of patients into clinical trials, instead offering a look into the world as it really is – with all the comorbidities, patient compliance issues, inadequate access to care etc. Official regulatory bodies responsible for evaluating healthcare interventions, like the FDA [12], EMA [13], NICE [14] and Polish AOTMiT [15] are increasingly interested in looking at the conclusions brought about by RWE to guide their decision making.

RWE can be used in multiple ways to inform various policies on the impact of interventions or burden of disease for the society. Examples of RWE applications are listed in Table 1.

Table 1 Examples of applications of RWE

Result of application of RWE	**Example measure**	**Source of data**
Clinical effectiveness	Complication rates or mortality in a specific diagnosis	Medical claims data
Treatment affordability for patients	Comparing the prices of available treatment options and juxtaposing them with median income	Effective prices in pharmacies, GUS data on wages
Adherence to treatment	Verifying purchasing of prescribed pharmaceuticals to a specific individual over time	Medical claims data
Cost of illness for the healthcare system	Linking together cost-generating events to the underlying cause or diagnosis	EMR
Indirect impact of disease on society	Loss of productivity of workers in the economy due to illness-related absenteeism	Social insurance data, EMR

Source: Own analysis

The application of RWE for assessment of health interventions and policies is widespread across the world.

In Germany RWE was used for example to evaluate the impact on the German healthcare system of appraising new digital applications [16], or to quantify the unmet need in diabetes [17]. In Italy, a database of prescription drugs dispensing allows for an in-depth analysis on the prevalence and incidence of psychiatric disorders [18]. In Estonia, data from a stroke registry enabled monitoring of patient outcomes following stroke treatment [19]. In Poland, numerous analyses utilizing RWE are published on the NFZ site via reports and dashboards, to expand the understanding of the health status and behaviors of Polish patients. Some of the recent publications focus on depression [20], ischemic brain stroke [21] and obesity [22].

Despite its attractiveness, RWE has shortcomings that inhibit its wider use and the generalizability of the conclusions across borders [23]. Kamusheva et al. (2022) classify the barriers into 4 areas: technical, regulatory, clinical/scientific and perceptional. The first category is related to organizational or financial capacity to curate and use the data. Regulatory barriers include lack of unified or standardized guidance on its use, lack of requirements, frequently changing regulation related to RWE. Clinical and scientific barriers relate to uniqueness of demographic, racial or genetic characteristics of the evaluated populations, differences in epidemiology, variations in disease severity, different setup of the healthcare systems that impact care delivery, lack of transparency in the design, execution and reporting of RWE-centered studies, among others. Finally the perceptional barriers include the uncertainty in the quality of the evidence and lack of trust in the results due to lack of access to the underlying data or the protocols of analysis.

Because of that, development of a “one size fits all” guidance that would be specific enough to address the underlying complexity of the research question or that would guarantee success regardless of the place of application is difficult if not completely unlikely. Instead, there are multiple facets of best practices [24-27] developed based on expert knowledge, case studies in specific disease, geographies and the setting of healthcare system.

Due to the cited shortcomings of RWE [28], data from clinical trials is still preferred by regulatory agencies in formal decision making. This is true mostly for drug registration or reimbursement. However, in fields where randomized clinical trial (RCT) data is scarce and difficult to

produce, RWE utilization is more popular. This is the case for non-pharmaceutical technologies, like applications and mobile health solutions, or orphan diseases, as well as activities aimed at prophylaxis and raising patient awareness.

At the same time, even in light of challenges on a supranational level, local application can still be extremely valuable. The dissertation focuses on the utilization of RWE in health policy-related decision making because of the potential it offers for the local healthcare system. In Poland, the availability of high quality RWD data sources are growing. Multiple institutions collect large amounts of information that has potential for evidence generation for matters related to healthcare. The databases owned by NFZ, ZUS or the MoH contain years' worth of data on the status and trends in the Polish population. With the advent of data science, including but not limited to machine learning, natural language processing and artificial intelligence algorithms it is becoming easier to analyze the information and connect it to external sources creating a comprehensive view of the issue at hand.

5. Aim of the thesis

5.1 Scientific aims of the thesis

With the increasing costs and persistent gap in health status and outcomes of the Polish population versus other countries, the healthcare system in Poland requires policy interventions aimed at improving outcomes and delivering more care to patients while maintaining fiscal prudence and dealing with increasing resource scarcity. Those optimization efforts need to take into account the interdependencies of the healthcare ecosystem and preferably address the issues at their root cause instead of the symptoms. Hence, it is not always the best solution to merely cut expenditures where they are highest.

This is why in this work the new evidence is presented on the ways in which optimization of pharmacotherapy can be utilized for the overall purpose of improving healthcare in Poland.

Secondary goals include: to encourage the utilization of RWE for decision making in healthcare, to specify the role of pharmacotherapy management in selected diseases (rare and prevalent); to explore the effects of insufficient effectiveness of pharmacotherapy and to analyze the financial aspects of pharmacotherapy management.

5.2 Research hypotheses

The series of articles aims to verify the following hypotheses:

H1. RWD can be used in guiding of health policy (Articles 1, 2, 3, 4)

H2. Properly functioning management of pharmacotherapy as a tool of health policy can bring clinical benefits for patients. (Article 1)

H3. Pharmacotherapy management can be used to generate savings in the healthcare system (Articles 3, 4)

H4. Effects of insufficient or underused pharmacotherapy may materialize in reduced worker productivity and reliance on social benefits. (Articles 2)

H5. Pharmacotherapy is not always used optimally in Poland at the moment. (Articles 2, 3)

H6. There are areas for improvement in pharmacotherapy in Poland that would be associated with clinical and cost benefits for patients and payers. (Articles 1, 3, 4)

6. Material and methods

The Articles included in the dissertation present an array of numerical methods of analyzing and presenting data, common in scientific literature on the topic. All articles utilize data representative for the Polish population.

6.1 Article 1

The first included publication covers the topic of effectiveness and costs of a drug program in patients with a rare genetic disorder, spinal muscular atrophy (SMA) in Poland. SMA, despite being a rare disease, is still relatively common and affects a considerable number of patients and their families in Poland. It is also one of the costliest rare diseases for the payer [29]. It compares the clinical effects of establishing access to treatment to two separate patient groups, and separately evaluates the costs incurred by the public payer for treatment of the total population suffering from the disease in Poland.

6.1.1 Data

In Article 1 the primary source of data was the databases of the National Health Fund (Narodowy Fundusz Zdrowia, NFZ), which contains information on all benefits granted to patients financed from public sources. Stored information includes patient identifier, patient age, patient

gender, benefit granted, date of benefit delivery, benefit provider identifier, cost incurred by the payer and other supplementary information. The NFZ database enables longitudinal tracking of selected patients throughout an analysis period. In this article, a specific population of patients was first selected from the general database, and later tracked across several years. The selection of patients of interest was based on a defined set of rules (number of visits of specific type, timing of visits, year of birth, etc.). all cost data for the selected patients where sourced from the database and aggregated.

6.1.2 Methods

To analyze treatment effectiveness in patients with SMA a retrospective natural experiment was conducted. Since access to disease modifying treatment has been established for patients only since January 2019, a comparative analysis of two separate cohorts of patients was selected (those born in 2014 and in 2019) and evaluated on two endpoints: all-cause mortality and onset of mechanical ventilation. The disease has a progressive nature – once a patient moves to mechanical ventilation, they do not experience improvement in their condition. Survival analysis and Kaplan Meier curves were used to describe the effect of the treatment on the total population of patients in the specific, distinct cohorts.

To analyze epidemiology of the disease in Poland as well as burden on the public payer, the cost data for the entire SMA population in Poland was retrieved from the NFZ database and aggregated by year and type of benefit received by the patient. Additionally, data on expenditures on the drug was sourced from publicly available NFZ reports.

Since NFZ is the sole payer in the public healthcare system, and patients with SMA require highly specialized care, it is assumed that the entire population of patients was captured in the analysis. As such, no statistical method other than descriptive statistics was used in the presentation of results.

6.2 Article 2

This publication analyzes the behaviors of prescribers and patients with depression or anxiety in Poland in the period before and during the COVID-19 pandemic, in terms of consumption of pharmaceuticals and utilization of social benefits (sick leaves).

6.2.1 Data

Two types of data were used in the analysis. One type of information was related to consumption of pharmaceuticals procured by patients in community pharmacies. The data came from IQVIA Pharmascope®, a syndicated proprietary database of the IQVIA corporation. It contains data on the specific SKU (Stock Keeping Unit) of products sold in pharmacies, the date stamp, and the value of the transaction. Various additional data on the product is available, including the active substance contained within, WHO classification of the product, manufacturer, reimbursement status of the SKU in the transaction, etc. The database has national coverage in Poland and is representative of the entire country. The pharmaceutical consumption data spanned from January 2018 to October 2021.

The second type of data came from the Polish Social Insurance institution (Zakład Ubezpieczeń Społecznych, ZUS) and it covered the duration and frequency of sick leaves taken by adult individuals in relation to their own indisposition caused by a diagnosis of psychiatric nature. Similarly, the data had national coverage since ZUS is the sole provider of this type of benefits in Poland. The sick leave utilization data spanned from January 2018 to April 2021.

6.2.2 Methods

Analytical methods employed in this article included descriptive statistics for the relevant subsets of available data, Correlation Analysis and Interrupted Time Series Analysis, to test for the impact of the onset of the pandemic on the mental condition of patients in Poland.

6.3 Article 3

The article covers the topic of generic substitution in community pharmacies in Poland, which is a practice of exchanging the product originally prescribed by a physician to an equivalent product from a different manufacturer. The reasoning behind this procedure is predominantly the cost difference for both patients and payers associated with brand name or copycat products.

6.3.1 Data

The data used for this study was the custom created database, which combined information from two sources:

1. E-prescriptions issued by physicians,

2. Dispensation data on actual transactions within community pharmacies.

Both data sources were in possession of the NFZ, and unique identifiers enabled the establishing of the connection between them to track the actual behaviors of patients.

Metformin, a commonly prescribed drug to treat the prevalent condition of diabetes, was used as a model drug to illustrate the scope and impact of the generic substitution phenomenon in the Polish system.

Regularly published official MoH reimbursement lists were used to assign the relevant prices to the products to calculate cost differences between the product prescribed and dispensed.

The data covered in this article spanned from January to December 2019.

6.3.2 Methods

Similarly, as in the case of previous articles, basic statistical analyses including descriptive statistics, percentages and aggregated values were used in results presentation.

6.4 Article 4

This article explores the treatment patterns of patients suffering from hypertension in Poland and focuses specifically on the instance of loose and fixed combinations of a commonly prescribed medications and its financial impact for patients and the public payer.

6.4.1 Data

The analysis relied in part on the proprietary software of IQVIA Corporation (formerly IMS Health), called the “LRx”, which is an application that analyzes longitudinal patient behaviors on the market based on the individual transactions recorded in community pharmacies across Poland.

Additionally, the entire market volume and value for hypertensive medication was sourced from IQVIA Pharmascope database. Reimbursement levels for specific SKUs were retrieved from the official reimbursement lists.

The data covered in this article spanned the period from January 2014 to August 2015.

6.4.2 Methods

In the description of the behaviors of the population treated for hypertension, the utilized tool classifies the patient into specific group depending on their purchase (treatment) history. This enabled an evaluation of the size of the regularly treated population along with a dynamic flow of patients from one therapy to another, initiations, and abandonment. Thus, selected groups were later examined for the economic evaluation of the behavior, which could also be named treatment strategy.

In Article 4 one specific case is analyzed, that of patients who purchase two active ingredients in distinct packs (defined as a loose combination) in comparison to the alternative, which was the purchase of the exact same active ingredients in a single pack. Price differences were analyzed from the perspective of both patient and payer.

7. Summary of the results

7.1 Article 1

In the analysis of the effectiveness of nusinersen before and after the introduction of the drug program two cohorts of 45 and 51 patients respectively were compared. The observed difference in mortality in children afflicted with the disease was a reduction by 25 percentage points, a statistically significant result. At the same time, when the focus outcome was extended to include induction of mechanical ventilation along with mortality, the difference between the two cohorts became insignificant. With the extended scope of outcomes, we found median survival of the control cohort to be 823 days, while the group subject to treatment did not reach the median point after 1382 days of observation.

When the analysis was extended to look at the entire treated population of SMA patients in Poland, at the end of the observation period 875 patients had had been treated within the drug program, 53% of whom had been male with a median age of around 16 years. A narrow majority of the patients were underage. The size of the population with SMA3 was roughly twice as large as either SMA1 or SMA2, for both genders.

Reimbursement of drugs was found to amount to about 37 million EUR annually, while the cost of healthcare benefits was around 4,5 million EUR. Treatment of patients with the most severe presentation of the disease consumed about 60% of resources despite pertaining to roughly 20-30% of the total treated population, depending on year. The importance of long-term care in the total costs

was inversely correlated with the severity of the presentation of the disease. We found that as the program progressed into the fourth year of its operation, the average costs per patient by type of service stabilized, indicating efficiencies in delivery of benefits.

As the overall healthcare benefit costs granted to patients included in the program did not increase with growing treated population, this indicates growing operational effectiveness of health services delivery with growing familiarity of specific providers of the needs of this patient group – improved service delivery pathways, moving of services from very cost intense inpatient treatment to other channels and optimization of care organization. Average costs per patient decreased from 10,711 euro per person per year to 5,481 euro in the third year, a 48% drop. This result was achieved despite reduced mortality, which meant that more patients requiring costly intensive care survived for longer.

7.2 Article 2

Depression affects a significant portion of the Polish population, with prevalence estimates ranging between 3.17% [30] - 3.85% [31] of adults. Simultaneously, the lifetime prevalence of anxiety attacks is estimated at 7% in the EZOP II study, equivalent to 1.3% annually. It is estimated that there are around 2.2 million people who have suffered from anxiety in Poland. While those conditions may share similar symptoms in selected areas, they do not always occur together. Comorbidity of those conditions has been verified to be substantial [32, 33], ranging from 33.7% up to 65%. This indicates that the overall population of depression and/or anxiety in Poland can range from 2.2 to 3.0 million people annually. According to the NFZ, around 1.38 million people took advantage of reimbursed products to treat depression and anxiety [34]. The discrepancy between those figures shows that a substantial number of people in Poland currently do not receive reimbursed treatment, indicating a potential therapy gap.

The situation was further complicated by the onset of the global pandemic, an event unprecedented in the history of modern healthcare systems. COVID-19 has been proven to create mental burden on populations globally, exacerbating existing mental conditions and inciting them in previously healthy patients. Article 2 describes the gap between the treated population and the productivity reduction caused by the focus disorders that were brought about by COVID.

No significant changes in behavior were observed on the pharmacotherapy side during the pandemic: the trend in consumption of antidepressant and antianxiety medication was found to be

strictly increasing at a pace of approximately 1% month to month. No differences were identified in the pre-pandemic period and since its outbreak, nor were there any differences between product groups. A gradual move towards larger doses purchased within a single pack was observed, indicating that some of the increase in consumption could have been associated with intensification of therapy, reducing the evidence pointing to introduction of new patients to treatment.

Sick leaves painted a wholly different picture. Before the pandemic there were roughly 70,000 sick leave notes issued for the diagnoses related to depression and anxiety in Poland monthly. Between January 2018 and January 2020, the number has been increasing at a pace of 0.44% monthly. When the pandemic started in March 2020, the number of sick notes grew to 107,000 in March 2020 and reached a peak in April 2020 at 132,000, later falling to a steady level of 91,000 monthly.

The levels of sick leaves issued due to depression and anxiety increased by 27%, a figure which excludes the peak associated with the onset of the pandemic which may paint a biased picture due to the uncertainty of the market that might have been reflected in the number of sick leaves issued. This result points to two explanations: that in areas where therapy was previously effective in sustaining a patient's ability to work, was no longer enough after the onset of COVID, indicating loss of treatment efficacy; that patients who had not been previously treated for depression or anxiety became ill without the induction of proper efficacious pharmacotherapy.

7.3 Article 3

According to the analyzed data, almost eleven million prescriptions for metformin preparations were dispensed in Poland, for a cumulative 19.6 million packs of various medicinal products containing metformin. As many as 75% of these prescriptions led to the dispensation of generic drugs, which altogether accounted for 70% of the total number of packs dispensed. The total cost of the dispensed metformin was 298.6 million PLN, of which 192.2 (64%) was covered by the public payer in reimbursement and 106.4 (36%) was covered by patients as out-of-pocket co-payments. The share of the generic drugs was 67% in total costs, with the rest going to the originator brand name product.

Despite the possibility of dispensing the drug with generic substitution, only 4% of all transactions took advantage of this mechanism. On average, substitution of the originator or other generic for a cheaper version constituted savings in the scope of 0.99 PLN per pack for the patient and 0.28 PLN for NFZ. Had substitution been optimized, so as to revert to the least costly available version

of the product, the savings could be extended to 1.78 PLN for the patient and 0.94 PLN for the public payer per pack. Cumulatively, the patients could reduce their spending on metformin preparations by 15.9% and the payer by 8.3%, so theoretically up to 33 million PLN per year on a single product. This result positively verifies hypothesis 1, that changes in the management of pharmacotherapy on societal level are associated with tangible financial effects.

7.4 Article 4

Ramipril was the most frequently prescribed angiotensin converting enzyme inhibitor (ACEI) in Poland for hypertension, with approximately 2 400 000 patients treated regularly. Its popularity was the primary reason this drug was chosen for further analysis. The second most popular drug – perindopril – was used by approximately 80 000 patients. From January 2014 to March 2015 the number of patients treated with ramipril grew month on month to reach a plateau in March and April 2014, followed by a slow decline.

The number of patients treated with fixed dose combinations was much lower with 30 000 and 25 000 patients receiving perindopril-indapamide and perindopril-amlodipine products, respectively. Ramipril-amlodipine combination, although not the most prescribed, was the most dynamically increasing group by patient volumes. Hypertension therapy was associated with considerable complexity at the time, due to multitude of combinations of available preparations and dosing.

Evaluation of the benefits of adopting a treatment strategy to reduce the number of products a patient is using was the focus of the latter part of the article. Switching a patient from a loose combination to a fixed dose combination is associated with clinical benefits of improved adherence to treatment, as well as reduced costs for patients and the public payer. When patients move from purchasing two separate packs of hypertension medication to a single pack containing a fixed dose combination the ultimate result is savings for both patient and payer, varying in level depending on the dosing of the drugs. Patient savings were higher when the switch occurred to generic formulations of ramipril and amlodipine fixed dose combination that to the originator. In case of the originator savings were larger for the public payer. Interestingly, the effect of savings generation did not hold for other fixed dose combinations of ramipril.

8. Discussion

Societal use of pharmacotherapy is a broad field that has far reaching implications in Poland that extend beyond the healthcare system itself. This dissertation aimed to frame pharmacotherapy as a key tool at the disposal of policy planners to improve quality of care, patient wellbeing, worker productivity and economic sustainability. It is also evident that the importance to utilize available data sources to plan, monitor and assess the effectiveness of pharmacologic interventions in order to adequately distribute limited healthcare resources to the greatest societal benefit is rising.

Article 1 looks into the currently implemented rare disease management program, targeting the most vulnerable members of the population. The disease affects not only the patient, but also has a large impact on their immediate surroundings because of the necessity to care for them on a permanent basis, thus impacting their carers' ability to hold employment. Provision of necessary healthcare interventions rests on a network of interdependent facilities that must coordinate between each other and be located efficiently enough to be available at the right time. Lastly, the burden on the public financing system is significant and requires oversight not to spiral out of control. The case of SMA shows that it is indeed possible to devise a system that improves on patient's health outcomes (reduces mortality) while costs remain at predictable rates and even decrease with improvements and knowledge gained over time. Newborn screening program [35] introduced in this field is an example of an approach that focuses on prevention and preparation ahead of time, instead of reactive actions only when the symptoms arrive. It is a clear instance of conducting a cost benefit analysis, where the costs of performing hundreds of thousands of genetic tests every year enable early induction to therapy that postpones the development of severe irreversible symptoms and mortality in case of very few patients.

Article 2 focuses on the connection between pharmaceutical consumption and worker productivity in depression and anxiety, disorders that touch a significant portion of the population in times of an unprecedented event of a global pandemic. COVID-19 was a disruption in the daily lives of people around the world and introduced an impulse not seen for a century [36]. Moreover, studies have been published detailing the scale of the mental health burden in Poland during the pandemic [37]. It created a natural experiment that enables a clear before and after analysis of behaviors. We found that whereas workers' behaviors were significantly and permanently affected by the pandemic, the purchasing of drugs aimed at combating those effects was not. This may be a symptom of an issue in the field of mental health that exists in Poland [38] that requires not only further investigation but

actions on the policy side. Instead of public financing for relatively inexpensive pharmacotherapy, we as a society bear the much larger cost of worker idleness and consequential reduction in economic productivity [39].

Data on numerous topics is becoming omnipresent. It is being collected at an unprecedented pace and scale, and it is being shared between multiple stakeholders, in many situations in real time. This free flow of information about all things health related offers a new perspective for shaping the incredibly complex ecosystem. It also fosters a new way of thinking about data collected in a particular field – it promotes a holistic rather than targeted approach. As an example, the connection between drug consumption and worker productivity enables the view of the link between patient's well-being and their performance in the workforce.

It is no longer enough to look at data on drug consumption on its own, since it also affects the pharmaceutical supply channel (pharmacies [40], wholesalers, mass market outlets), and thus may have consequences in advertising, dietary supplements [41] and market concentration among large private retail chains. In Article 3 it is argued that improved use of available policy tools, here in the form of enforced generic substitution, would generate positive impact for patients and payer [42]. Similar conclusions were reached in Article 4, where it was demonstrated how a choice of a combination therapy was superior in terms of cost and patient adherence to alternative approach.

Naturally there are limitations of the presented analysis. In Article 1, the limitation is related to the heterogeneity of the patient population in terms of disease severity and duration. It is possible that some cases had been missed due to mortality before diagnosis. Moreover, the cohort comparison was limited to only two groups, arbitrarily differentiated by year of birth. More nuanced analysis of subpopulations would be warranted in this case to verify the sensitivity of the results. In Article 2, the analysis was conducted while the pandemic was still ongoing, thus limiting the estimation of the full effect of the described phenomena. Secondly, due to the aggregate nature of the data it was not possible to detect underlying granular trends. The monthly format of the data inhibited a more detailed and sophisticated approach to analysis. Conclusions in Article 3 were formulated solely on an example of a single medicinal product, which despite its obvious importance to the healthcare system, may not be unconditionally representative of the full spectrum of the impact of generic substitution or its economic consequences for Poland. Focus on e-prescriptions may have contributed to the underrepresentation of some groups of patients or behaviors, which would not have been accounted for in the analysis. Limitations of Article 4 include lack of formal effectiveness measures to assess the

impact of switch from loose to fixed dose combinations on patients' treatment adherence and a somewhat narrow, targeted approach looking on a single treatment option in an environment where multiple strategies are at doctors' disposal.

The scientific inquiry presented in this thesis adds empirical evidence on selected health-related issues facing the Polish population and presents methodologies and tools that can be employed to monitor and evaluate healthcare policy programs or interventions aimed at addressing those issues. Specifically, for rare diseases or life-saving medication the evaluation of real-life treatment effectiveness measured by patient mortality can be a compelling argument in deliberation on reimbursement conditions. For mental health issues that can be influenced by geopolitical factors, of which the recent pandemic can be an example, it is valid to conduct verification from multiple angles – including not only patients' treatment adherence but also their activity in the workplace. Thirdly, as treatment compliance is a key factor in proper disease management, the financial aspect of maintaining affordability of drugs and promoting solutions that offer economic benefits to patients on top of clinical ones is an example of a win-win scenario in the setting of the entire healthcare system.

9. Conclusions

The research presented in this dissertation provides additional evidence from clinical practice in Poland on the impact of RWD on health policy planning. Real-World Data can be successfully used for this purpose in a number of ways, verifying **hypothesis 1**: First, to monitor the effectiveness of already established initiatives, like drug programs aimed at treating orphan diseases, as presented in Article 1. The investigation of the achieved clinical benefits can serve as argument in reimbursement discussion with manufacturers of drugs or become a reference for future agreements also in other therapy areas, where conditional reimbursement would be considered. Second, to maintain control over the budget and monitor expenditures, as highlighted in Article 1, where the longer-term cost accrual compared to the growing size of the treated population proves that the program becomes predictable in terms of costs and therefore is easier to plan for in the future. Third, RWE is a useful source of information for constructing business cases for the justification of new policies or investments in the healthcare space, as it enables the identification of current gaps and unmet needs, as shown in Article 2 and Article 4. By approaching an issue like depression or anxiety from two angles, treatment, and worker productivity, it is possible to pinpoint the existing mismatch between the two. Furthermore, the underutilization of pharmaceuticals or the limited popularity of the superior option,

like fixed-dose combinations, frames the problem to be addressed in awareness, education for both patients and HCPs. Finally, RWE can be a prime source for calculation of the expected impact of interventions, as presented in Article 3. Here, by mapping the current behaviors of patients and prescribers it is possible to estimate the financial effect of incentivizing the move from one pack to another. By further juxtaposing the financial gain against the costs of conducting the initiative, an informed decision can be taken on its viability.

Effectively managed and efficiently functioning pharmacotherapy, like the one described in Article 1, can bring clinical benefits to patients, which provides verification for **hypothesis 2**. In this analysis, the hypothesis is tested on a very narrow and highly specialized indication of SMA, which touches a small number of patients. However, the multifaceted approach employed in this case, starting from screening for appropriate candidates for treatment, providing therapy to children before symptom onset and longer-term monitoring shows that the holistic approach is associated with better clinical outcomes.

To further build upon the point of the benefits of proper pharmacotherapy, evidence is provided that the management of pharmacotherapy on a societal level also may have a positive effect on the payer's finances, in accordance with **hypothesis 3**. As shown in Articles 3 and 4, modification of patients' current therapy towards preferrable options available on the market may lead to lower costs for both patients and the financing body. These moves would be made within the space of the current therapy and would simply take advantage of differences in generic drug pricing, or the resulting price impact of loose or fixed dose combinations.

While it was shown that advances can be made within the currently treated population, the untreated or inappropriately treated one will generate costs that may be invisible to a single public entity, like the NFZ. The example of patients in Poland dealing with depression and anxiety described in detail in Article 2 shows that despite increasing consumption of medication, the underlying trends do in fact point to an insufficient dynamic in the field of pharmacotherapy, and thus, to the existence of a group of patients who are not benefitting from the available options. This effect materializes only when additional information is taken into account, here in the form of social benefits and worker productivity. The described negative effect allows for the positive verification of **hypotheses 4 and 5**.

Since flaws in the current state were identified, it is only natural for the opportunity to correct those to arise, as stated in **hypothesis 6**. The evidence in Article 2 points to the potential of reducing expenditures on social benefits and sick leaves in Poland. On top of generating savings as mentioned

above, increased utilization of generic substitution and switching to FDC described in Articles 3 and 4 respectively could offer additional benefits to the population through increased adherence to treatment, which in turn results in better management of the disease and reduction of progression management costs.

10. Practical implications of the thesis

The results presented in the thesis showcase how pharmacotherapy can be used as a powerful tool for health policy to achieve important societal benefits:

- Reduced costs for patients
- Reduced costs for public payer
- Improved healthcare outcomes
- Improved adherence to treatment
- Reduced costs for social insurance
- Improved worker productivity through reduction of illness related absence

The presented points cover a wide range of applications for pharmacotherapy as a health policy tool, from cost intensive rare disease management to commonly occurring chronic diseases.

An increased focus should be put on securing and appropriate access to care and diagnosis, optimal therapy selection that would foster adherence, promotion of generic substitution aimed at reduced costs for the system and increased affordability for patients.

Some of the key barriers mentioned include insufficient patient education and awareness of the benefits of pharmacotherapy, unsupervised abandonment of therapy and insufficient promotion of generic substitution as a tool of cost reduction. Further emphasis should be put on physicians to increase the use of pharmacotherapy in mental disorders as a means of reducing the burden of sick leaves on both workers and the economy, as well as prescribing of medication that offers economic benefits and thus fosters treatment compliance.

In case of rare diseases, investment in newborn screening and comprehensive care from the moment of birth is a valid tool that brings about clinical benefits in the form of reduced mortality as well as manageable cost burden on the payer side with added benefit of continuous improvement and optimization of spending with growing familiarity of the processes.

The use of RWE for the purpose of measuring, evaluating and analyzing healthcare interventions and policies should be strengthened, by enabling researchers to gain access to the data

from multiple sources, to aid the decision makers in taking timely actions for the sake of improving the productivity of the Polish healthcare system.

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12. List of Tables

13. List of Figures

14. Appendices

14.1 Appendix 1: Article 1

Krupa, D., Czech, M., Chudzyńska, E., Koń, B., & Kostera-Pruszczyk, A. (2023). Real World Evidence on the Effectiveness of Nusinersen within the National Program to Treat Spinal Muscular Atrophy in Poland. Healthcare (T. 11, Issue 10, s. 1515). MDPI AG. https://doi.org/10.3390/healthcare11101515

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Article

Real World Evidence on the Effectiveness of Nusinersen within the National Program to Treat Spinal Muscular Atrophy in Poland

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Abstract: Background: Spinal muscular atrophy (SMA) is a debilitating neuromuscular disease resulting in children's mortality and disability. Nusinersen is available to all SMA patients in Poland since 2019. Aim: To compare mortality or disease progression to mechanical ventilation in two patient cohorts before and after the program's introduction. Additionally, to describe the patient population treated with nusinersen and costs incurred by the public payer. Methods: We used the National Health Fund (NHF) database to identify patients born in either 2014 or 2019, who received at least two health services with an ICD10 G12 diagnosis. Outcomes were time to event: death or first mechanical ventilation. We identified all benefits received by nusinersen-treated patients, between 1 January 2019 and 31 May 2022. Results: Children with SMA born in 2019 had significantly lower mortality in the first years of their lives than children born in 2014. Approximately 875 patients (all age groups) were treated with nusinersen in the analysis period. The cost of causal drugs in this period amounted to €51.4 million. The cost of healthcare benefits amounted to €14.9 million. Conclusions: The drug program to treat SMA improved patient care in Poland. The NHF database was a reliable source to monitor resource-intensive therapies' costs, demography, and selected patient outcomes.

Keywords: spinal muscular atrophy; real-world evidence; nusinersen; therapy costs; budget impact

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1. Introduction

Spinal muscular atrophy (SMA) is a debilitating neuromuscular disease, caused by mutations of the Survival Motor Neuron (*SMN1*) gene located on chromosome 5q13 [1]. The mutation results in a deficiency of the SMN protein, which leads to the death of motor neurons in the spinal cord. The *SMN1* gene has a nearly identical copy to the *SMN2* gene. The number of copies of the *SMN2* gene is a strong phenotype modifier, and in most patients is inversely associated with disease severity. The disease is characterized by degeneration of lower motor neurons, which leads to progressive muscle weakness and atrophy. Age of onset of symptoms and highest achieved motor milestones led to the definition of subtypes of the disease [2]: SMA1 is symptomatic in infancy, up to 6 months after birth. Children with SMA1 never achieved the ability to sit unsupported; SMA2 patients become symptomatic between the ages of 6–18 months and could sit but never walked unsupported; patients with SMA3 can walk without support, and many lose ambulation in the course of the disease. SMA4 patients are diagnosed in adulthood and present with limb-girdle weakness. Historically, the median age at reaching the combined endpoint of death, or at least 16 h/day of respiratory support in SMA1, was 13.5 months [3].

The incidence of SMA in Europe was reported as 1 in 3900–16,000 live births [4]. The prevalence of the disease is estimated at 1–2 cases per 100,000 people [2]. With improved access to genetic testing and the introduction of newborn screening programs, accurate

epidemiological data become available. The estimated incidence of SMA in Poland is 1:7356 live births [5]. The approximate SMA patient population size has been estimated at 1100 cases [6].

Up until recently, only symptomatic management and palliative care were available for SMA patients. The first disease-modifying agent, nusinersen (Spinraza®, Biogen) was granted marketing authorization by the Food and Drug Administration (FDA) in the USA in 2016, and by the European Medicines Agency (EMA) in 2017. As of 1 January 2019, the drug has been made available in Poland through a dedicated drug program to patients of all ages, with all SMA types, irrespective of the symptom severity or *SMN2* copy number [7]. In September 2022, the available treatment catalog was extended to include further entries into this clinical space: onasemnogen abeparvovec (Zolgensma®, Novartis) and risdiplam (Evrysdi®, Roche).

A national screening program for SMA in newborns was introduced in Poland in April 2021, and gradually implemented across the country. Since March 2022 it includes every newborn (opt-in necessary) [8].

The clinical effectiveness of therapy with nusinersen in our country has been reported before [6]. None of the treated patients were discontinued due to ineffectiveness, and in most cases a significant functional improvement was observed, measured by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) or the Hammersmith Functional Motor (HFMSE) Scale Extended, as appropriate for the patient's age and baseline function. The therapy was well tolerated and effective, which provides further rationale for introducing the program. We intend to further extend that conclusion by examining the impact of therapy on patients' overall survival.

The aim of this study is to describe the demographics of the SMA patients treated in Poland, the costs incurred by the public payer, and the effectiveness of the treatment of SMA in clinical practice.

2. Materials and Methods

The primary data source for the epidemiology and cost analyses was the claims database of the National Health Fund (pol. Narodowy Fundusz Zdrowia, NFZ), which contains information about all healthcare benefits financed from public sources. Since the NFZ is the sole public payer in Poland, and in the absence of significant private medical insurance, especially in a highly specialized and costly treatment such as SMA therapy, it is reasonable to assume that the database covers the entire population of interest. The NFZ claims the database enables longitudinal patient-level analysis based on database-wide unique identifiers. Therefore, it enables tracking of selected patients across the entire publicly financed healthcare system, including prescription drugs in community pharmacies, medical device use, inpatient care, and specialty outpatient care. Instances where benefits are financed via flat rates, such as primary care, emergency room (including ambulances), or health resort treatments, where assigning a financial figure to a specific benefit granted to a specific patient is not possible, are excluded from analysis.

We analyzed the demographics of SMA patients enrolled in the drug program, from its establishment in January 2019 up until May 2022 (cut-off date). The same period was used to analyze costs associated with the program. The date of first reported administration of the drug was adopted as the date of enrollment, all nusinersen administration dates were reported to the NFZ for each patient. Both cost and demographic data have been augmented with details of the SMA type sourced from a dedicated platform created by the payer for the monitoring of the drug program. It contains additional patient information besides the claim's records stored in the NFZ.

To analyze the real-world effectiveness of therapy with nusinersen in Poland, we adopted a targeted approach, with the objective to select two groups of patients whose only identifiable differentiating characteristic was access to treatment. We compared two cohorts of patients, children born in 2014 and 2019, where the latter cohort is assumed to have had access to treatment from birth (as they were born after the introduction of the program)

and the former cohort who only acquired access at a later age when the program was introduced in Poland. Both cohorts were eligible to receive the treatment with nusinersen upon the program's introduction. We looked at two major endpoints: overall survival (OS) and time to progression, defined here as either the first reported instance of mechanical ventilation or death. The reasoning for narrowing down the population to the two distinct cohorts was to control for potential confounding factors related to patient characteristics and accessibility of specialized care within the setting of the Polish healthcare system.

Identification of patients with SMA from distinct cohorts was based on two separate records of ICD10 code G12.X diagnosis in patients' medical history. The diagnosis had to have been issued in a hospital or by a neurology specialist. The patient was later followed up based on his or her unique identifier, regardless of other concomitant diagnoses or reasons for interaction with the public healthcare system. It is the same approach as published in [5], that reduces the probability of including patients with a single or unsure diagnosis. Retrograde analysis of patients with SMA included in the drug program of patients based on inclusion into the drug program would be insufficient since many of the patients born in 2014 have died or were put on mechanical ventilation before nusinersen was available. Therefore, they would have been excluded from the analysis, inflating the impact of therapy compared to those who are tracked with confirmed diagnoses from birth.

3. Results

3.1. Effectiveness

We identified 45 patients born in 2014 who have had at least two separate healthcare services recorded within the NFZ database with the ICD10 code G12 and its extensions. Applying a similar methodology, 51 patients born in 2019 were included in the analysis. Up to the data lock date set on 31 May 2022, there have been eight deaths in the 2014 cohort and two in the 2019 cohort. On top of that, 20 patients from the 2014 cohort were administered any duration/day of mechanical ventilation compared to 23 from the 2019 cohort.

Figure 1 presents the Kaplan Meier curves for mortality within the two groups—patients born in 2014 and patients born in 2019. Out of children born in 2014, 72% of the cohort survived past their fourth birthday. No events were recorded for the children between the ages of four and eight. In the younger cohort, 97% of the cohort reached the three-year mark. The difference in overall survival is statistically significant at $p < 0.05$ (test statistic of the Log-rank test $X^2 = 4.9$, $p = 0.03$).

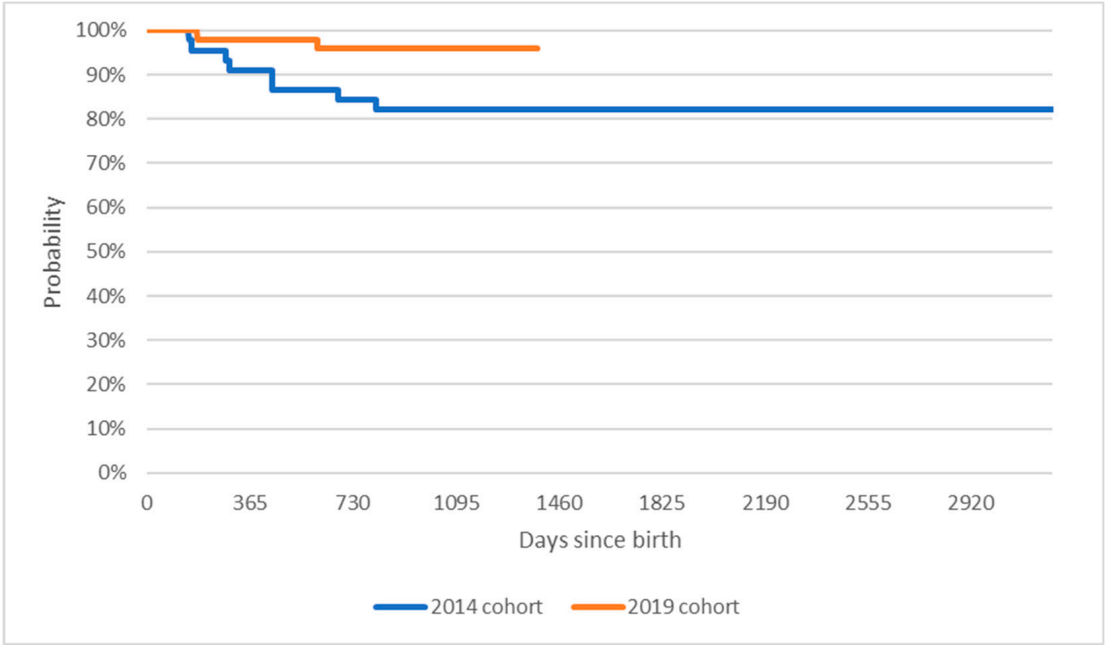

Figure 1. Kaplan-Meier curves comparing time to death of patients born in 2014 or 2019.

While the difference in mortality is significant, when survival analysis is extended to include mechanical ventilation, as presented on Figure 2, the difference in results between the cohorts becomes insignificant (p = 0.93, test statistic of the Log-rank test X^2 = 0.01), as presented.

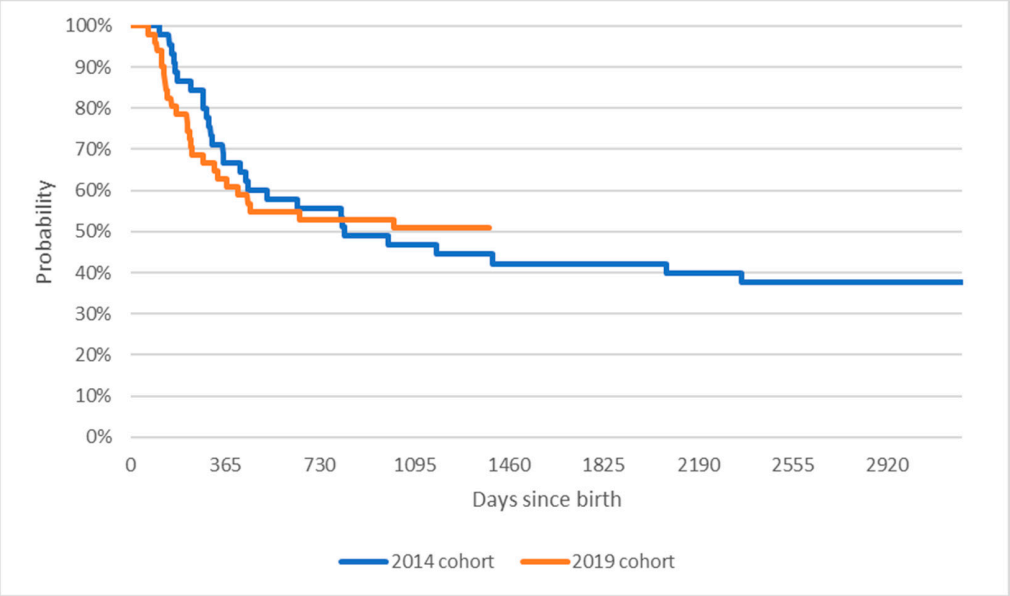

Figure 2. Kaplan-Meier curves comparing time to death or mechanical ventilation of patients born in 2014 or 2019.

Median survival for patients in the 2014 cohort was 823 days, or two years and three months. For the 2019 cohort, median survival was not observed as of the cutoff date of day 1382 since birth.

3.2. Demography of the Treated Cohort

In the period between January 2019 and May 2022, 875 patients have been included in the drug program and treated with nusinersen. As stated above, the program is dedicated to all patients with genetically confirmed SMA diagnosis; therefore, the described population is assumed to be equivalent to the total known patient population in Poland at the time.

Out of the total population, 53% were male and 47% were female. The average age was 21.7 years for males and 21.3 for females. Furthermore, 53.7% of male patients and 51.6% of female patients included in the program were under 18 years of age. The differences between the groups were not statistically significant. The detailed split is presented in Table 1.

Table 1. Demographic characteristics of patients treated within the drug program.

Characteristic	Male	Female	*p*-Value
Patient count	464 (53%)	411 (47%)	
Mean age (range)	21.7 (0–70)	21.3 (0–69)	0.77
Median age	16.2	16.0	
% under 18	53.7%	51.6%	0.61
Patient count by SMA Type:			0.17
SMA 1	117	101	
SMA 2	100	111	
SMA 3	237	189	
presymptomatic	10	10	

In 2019, the first year of the program, 442 patients were included in the treatment: 137 patients had SMA type 1, 105 had SMA2, and 196 had SMA3. Four patients started treatment presymptomatically. The size of the treated population by SMA subtype in subsequent years is presented in Figure 3. The share of SMA1 patients declined from 31% in the first year to 22% in the most recent period. The share of treated SMA2 patients was constant throughout the period at 24% of the population. In 2022, a little more than half of the treated population had been diagnosed with SMA3.

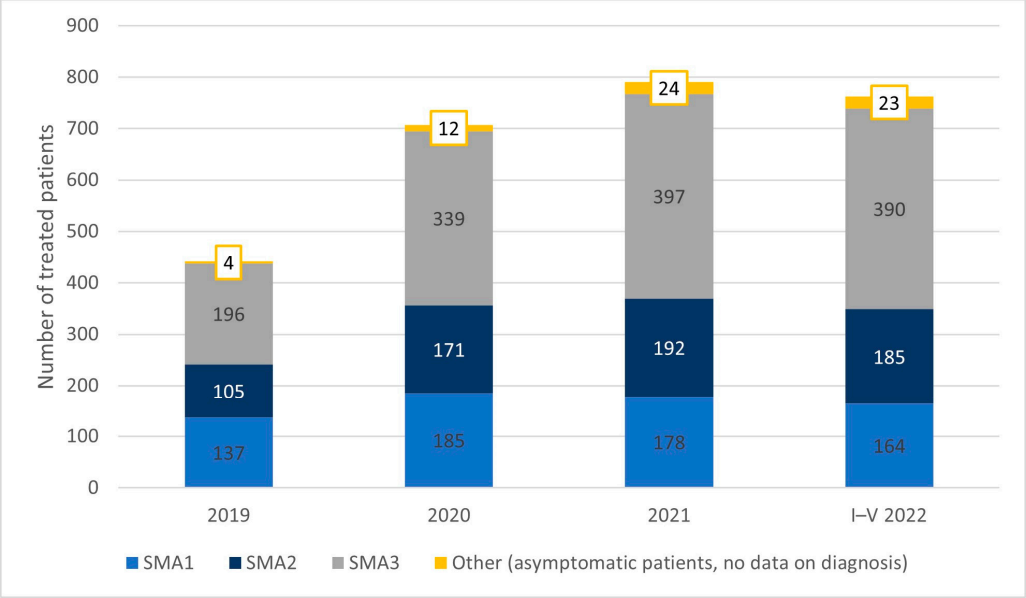

Figure 3. The population of patients treated with nusinersen within the drug program, 2019–May 2022.

As mentioned earlier, in the first year of the program, 442 patients started treatment. In subsequent years, there were 280, 134, and 19 initiations respectively (up to the cutoff date). There have been 15 treatment discontinuations in 2020, 50 in 2021, and 48 in the first five months of 2022. The size of the treated population at the cutoff date was 762. Figure 4 presents the flow of patients within the program since its onset.

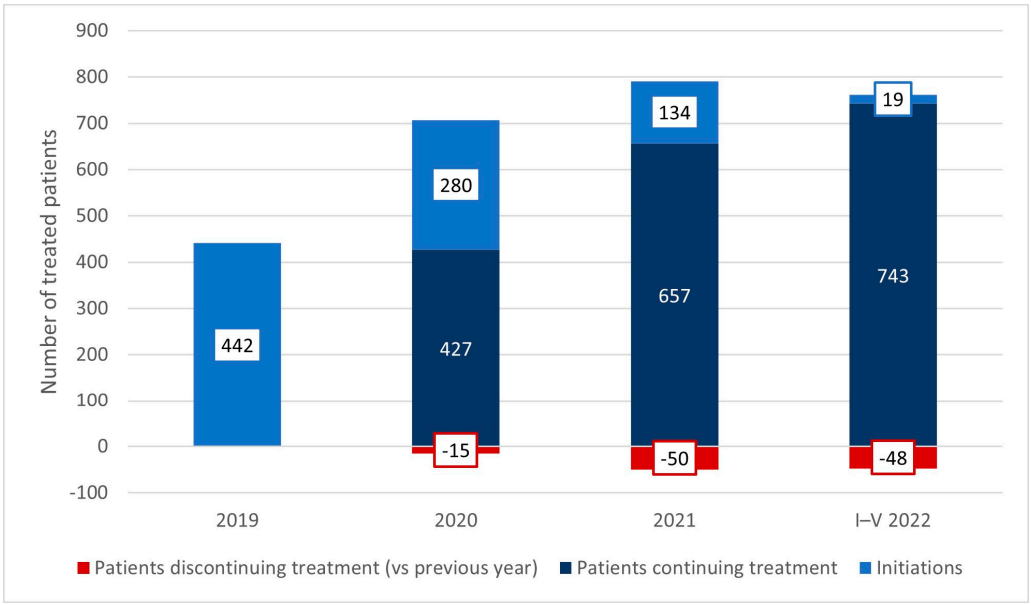

Figure 4. The flow of patients within the drug program, 2019−May 2022.

3.3. Costs

The direct medical costs associated with the treatment of spinal muscular atrophy covered within the public system are the costs of disease-modifying therapy and the costs of healthcare benefits granted to patients.

Between the introduction of the drug program and reimbursement of the first disease-modifying therapy in Poland in January 2019 and May 2022, the costs of medication amounted to 118 million Euro—13.96 million in the first year, 29.8 million in the second year, 36.86 in the third year, and 37.46 million in the first five months of the fourth year of reimbursement, as presented on Figure 5. The unit price of the product is most likely covered by a confidential agreement between the market authorization holder (MAH) and the Ministry of Health (MoH) [9]. Therefore, while the total cost of therapy is reported in public sources, the exact figure per patient is not known, as the nature of the agreement is not disclosed.

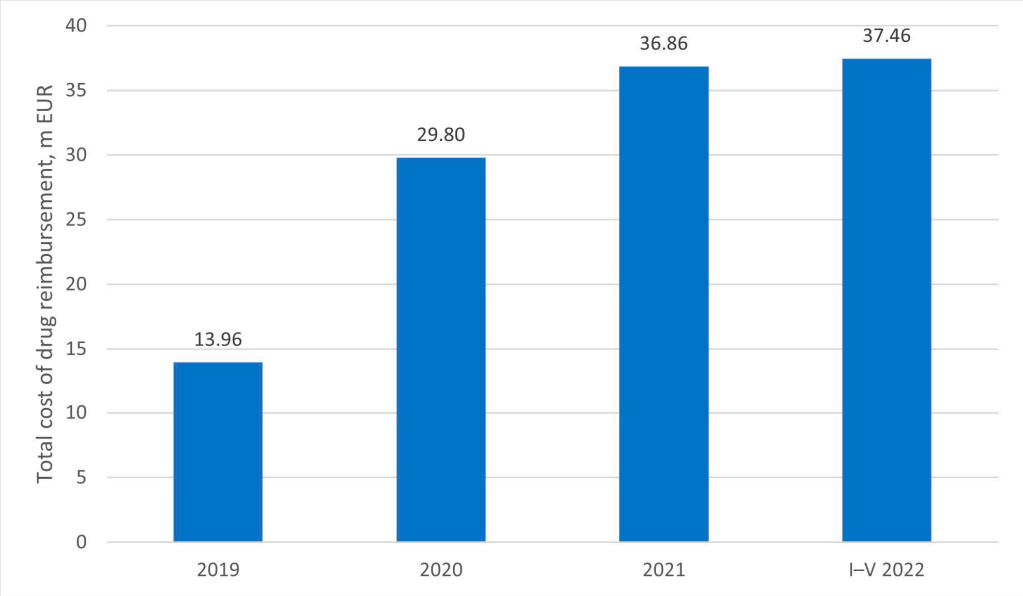

Figure 5. Cost of reimbursement of nusinersen within the drug program.

Costs of healthcare benefits were aggregated at the individual patient level, starting with the identification of all unique patients who have received the drug within the drug program, and the selection of all benefits reported within this population. The healthcare benefits were subsequently grouped into the following categories:

- Outpatient specialist care (excluding psychiatric care and medical rehabilitation)
- Inpatient care (excluding psychiatric care and medical rehabilitation)
- Benefits related to the drug program (diagnostics and administration of the drug, excluding the cost of the active substance)
- Long-term care
- Medical rehabilitation
- Palliative and hospice care
- Reimbursement of prescription pharmaceuticals, special foods, and selected medical devices (blood glucose strips and dressings, needles)
- Reimbursement of medical devices

The total cost of healthcare benefits granted to patients within the same period amounted to 14.86 million euros. The largest cost driver among benefits was long-term care, which cumulatively accounted for 47% of the total cost. The overall cost structure can be characterized as relatively stable. The year 2020 may be treated as an exception due to the unprecedented situation related to the coronavirus pandemic, which resulted in restrictions on the accessibility of healthcare services and potential deviations in reporting

benefits. Despite the decrease in the cost of benefits in 2020, attention should be paid to the fact that the population of patients who were offered treatment increased significantly. Figure 6 presents the detailed split of healthcare benefit costs between January 2019 and May 2022.

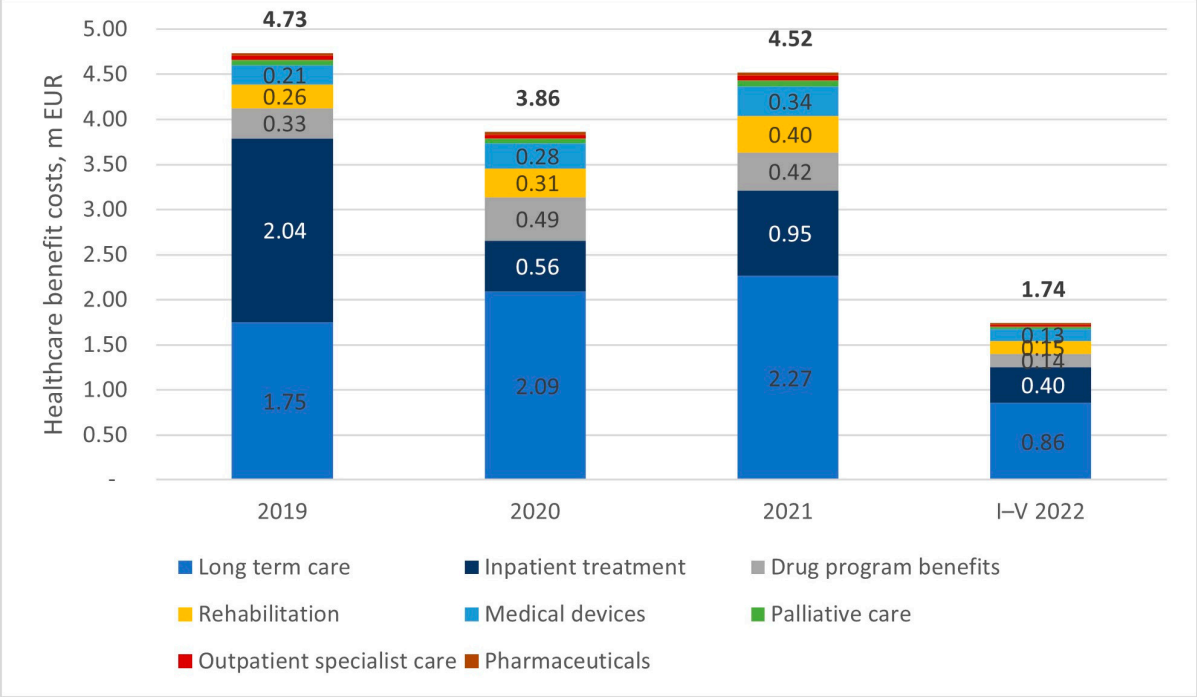

Figure 6. The detailed split of healthcare benefit costs between January 2019 and May 2022.

As previously mentioned, the types of SMA are differentiated by the course of the disease and the severity of symptoms. SMA1 manifests at the earliest stage of a child's development and is the most severe, while SMA 3−4 have a chronic, milder course. This is also reflected in the cost of caring for patients with specific types of diseases. Although SMA1 patients constitute between 20 to 30% of the treated population within the Polish drug program (depending on the year of analysis), their treatment accounts for nearly 60% of the total cost. A detailed breakdown of disease types and share in total costs is presented in Figure 7.

Long-term care accounts for almost 60% of the cost of care for patients with SMA1. In the case of SMA2, it is 38%, and for SMA3 it is just over 16%. This is related to the more severe course of the disease of these patients, and thus much greater patient needs for this type of service. Regardless of the type of disease, hospital treatment accounts for about a quarter of the total cost. For the group of patients with SMA3, costs related to the drug program are an important cost item, i.e., the costs of diagnosis, monitoring, and administration of the drug. In more severe forms of the disease, SMA types 1 and 2, this item has a decreasing share in the total costs. Patients with SMA3 use medical rehabilitation services to a relatively greater extent. A detailed breakdown of the shares of individual categories in the total costs of patient care is presented in Figure 8.

The average cost of treating a patient within the drug program decreased significantly from the onset of the program, where it amounted to almost 10,711 euros annually, down to 5481 in 2022 (full-year extrapolation from partial data covering Jan–May). Figure 9 shows the average costs in individual categories per patient treated in the drug program. After the first year of the program's operation in Poland, stabilization of the costs of treating a single patient in all categories is observable. Long-term care benefits remain the largest cost, averaging around three thousand euros per year. The cost of hospital treatment is about two thousand euros per year. The costs of a patient's participation in the drug

program amount to approximately 600 euros, similar to the costs of medical rehabilitation and medical devices. The average costs naturally vary by disease subtype, as healthcare benefits for patients with SMA1 amount to an average of 15,611 euros per year, for SMA2 to 6160 euros, and for patients with SMA3 to 2653 euros per year.

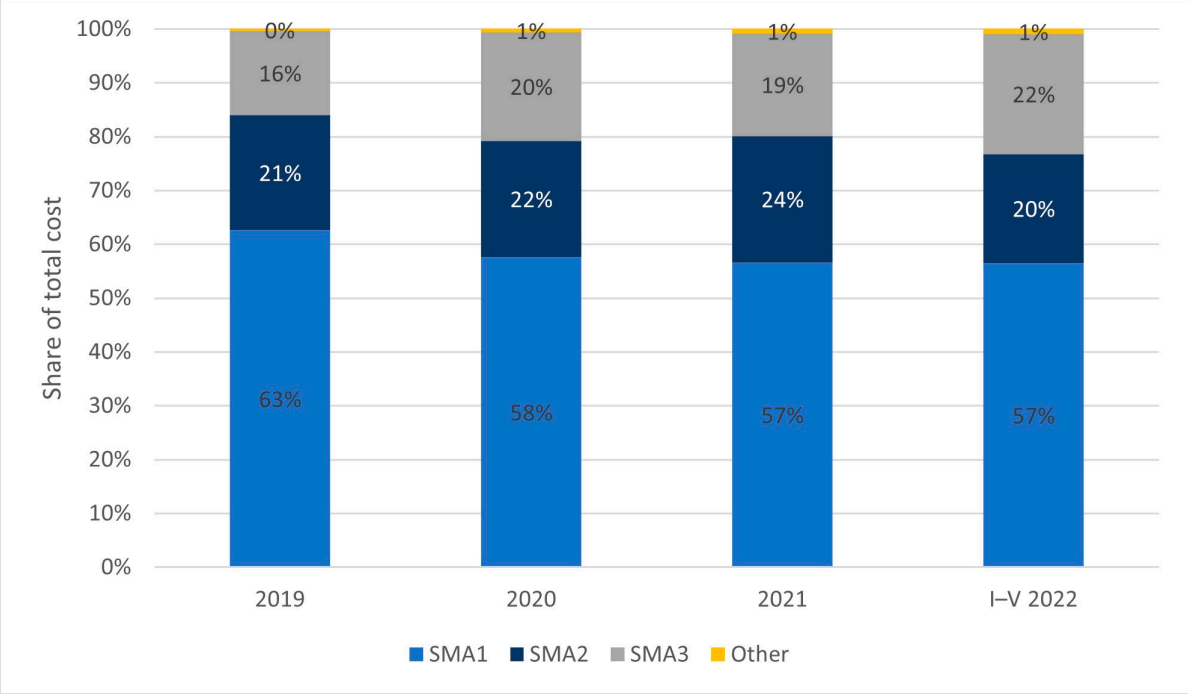

Figure 7. Split of healthcare costs by patients' subtype of SMA.

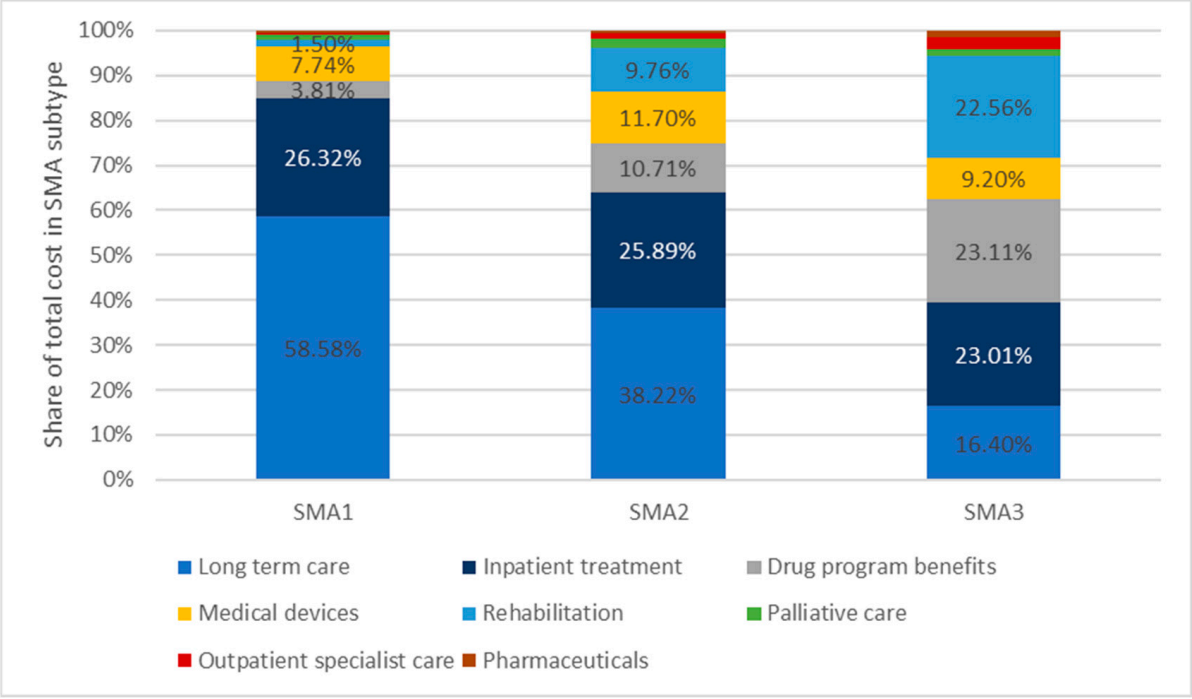

Figure 8. Costs covered by the public payer by healthcare benefit category between January 2019 and May 2022 by subtypes of SMA and types of care.

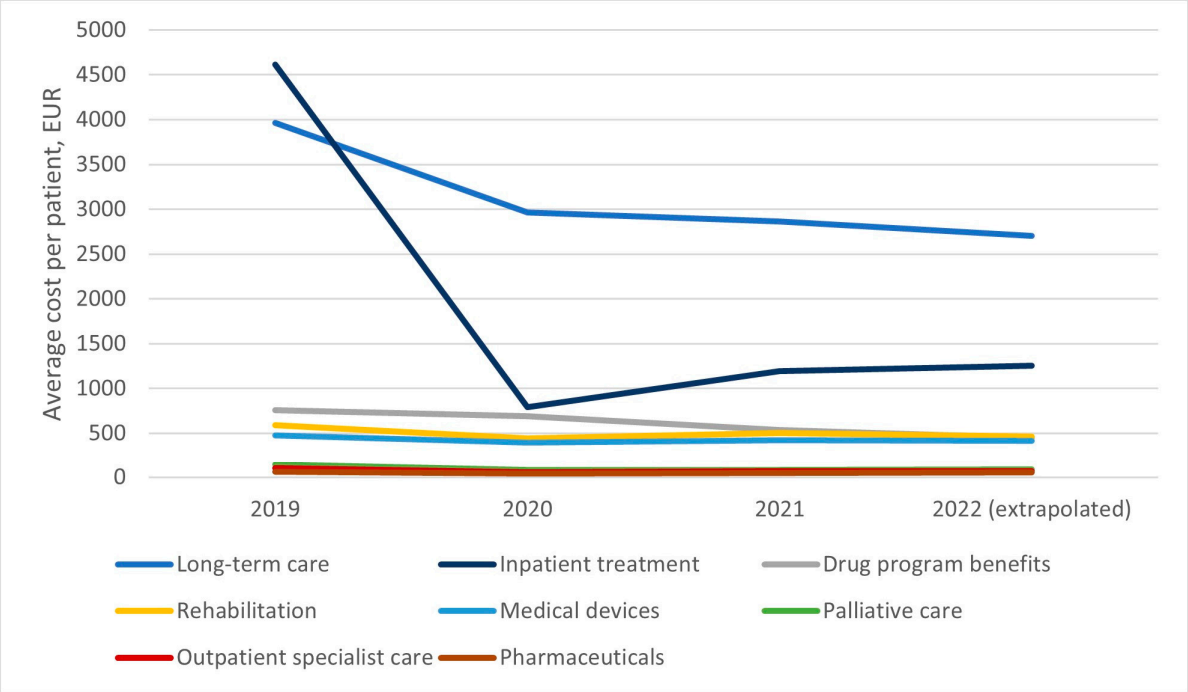

Figure 9. Average healthcare benefit cost per patient treated within the drug program. Note: * Data for 2022 have been extrapolated for comparability with previous periods. Available data cover the period from 1 January 2022 to 31 May 2022.

4. Discussion

This is the first study to comprehensively describe Polish SMA patients in terms of treatment and care costs. A key strength of the data presented herein is the fact that they pertain to the total population of patients with SMA. Data on Polish patients were analyzed previously [5] and focused on the epidemiology and standards of care for patients with SMA before the initiation of the drug program, which granted access to the first causal treatment to all patients. This work builds on results published there, as we greatly extended the size of the population covered.

Our results suggest that the measures recently introduced in Poland to screen, diagnose, and treat patients are effective tools for managing this debilitating disease.

Firstly, our results confirm that treatment with nusinersen leads to a significant reduction in the overall mortality of children with SMA in our real-world cohort. It was previously demonstrated in the setting of a prospective, strictly controlled clinical trial [10,11]. Inclusion criteria for the drug program in our country allow to start treatment in patients across the complete SMA severity spectrum, also those with symptoms more advanced as compared with clinical trial inclusion criteria. Overall, out of children born in 2014, 72% of the cohort survived past their fourth birthday. In those born in 2019, 97% of the cohort reached the three-year mark. Interestingly, we found no difference between treated and untreated cohorts in terms of progression to any duration/day of ventilation. This may suggest that advances in therapeutic options and awareness of SMA can extend a patient's life but are not always successful in postponing the onset of ventilation. It may also be because the drug program requires frequent evaluation by a multidisciplinary team, which may trigger the pro-active introduction of ventilatory support, for fewer than 16 h/day. The data collection method did not allow us to verify the number of hours of mechanical ventilation received. It has also been demonstrated that functional improvement with nusinersen treatment builds up with consecutive doses; thus, possibly longer observation is needed [6,12].

Secondly, we observed a dynamic increase in the number of patients treated within the drug program during the first two years since the reimbursement decision. We hypothesize

that the drug program included most older patients with SMA and that most new initiations will be likely due to new diagnoses, including newborns identified by the nationwide screening program. This strengthens the role of rare disease registries in trial- and treatment readiness. Our SMA TREAT NMD Registry facilitated planning treatment [13,14]. The size of the treated population is relatively large and is likely to grow in the future, as current patients will continue therapy and new initiations will occur at a steady pace related to the natural incidence of the disease. This enables policy planners to adequately plan capacity in neurology centers in the country in terms of resources.

Thirdly, we conclude that caring for patients with spinal muscular atrophy is cost-intensive, compared to the average cost of patient care in Poland, which amounted to 582 EUR in 2021 [15]. It is, therefore, reasonable to monitor and analyze costs to maintain control over them and identify anomalies (e.g., sudden increases) early. The analysis of the costs of care for all patients included in the program until May 2022, as previously presented, suggests that the payer's expenses per patient were stable after having decreased after the introduction of the drug program. In the period 2019–2021, average NFZ expenses per patient increased by a compound annual growth rate of 3.9% [15]. This may indicate the development of certain standards in dealing with patients on a national scale.

Our study has several limitations. The treated cohort is heterogeneous in terms of age and severity, and while we report on costs by SMA type, we did not analyze the dynamic of costs depending on patient age. In the effectiveness section, we aimed to address the heterogeneity by comparing groups of the same age. Due to the limited scope of information in the claims database, we could not stratify the cohorts by disease severity. Furthermore, the duration of observation is relatively short as compared with the natural history of SMA 2−3, or chronic types. It is possible that some severe SMA1 neonates who were born with the disease died before confirmatory diagnostics. The inability to identify those patients within the database, and their resulting exclusion from analysis, limit the mortality analysis but should have a similar influence on data from 2014 and 2019 (pre-newborn screening), as a result, older cohorts have milder phenotypes resulting in improved survival. For this reason, we chose a recent cohort to provide a comparison to those born before and after wide accessibility of treatment. It is possible that some patients that should have been included in our analysis have been missed.

Another limitation is related to the selection of cohorts—we compare only two groups of patients, where a broader, more nuanced analysis by subpopulations would be warranted to perform sensitivity analyses on the presented results. The study presented herein is a retrospective analysis of an insurance database, which is covered by strict privacy clauses that prevent the identification of individual patients, limiting the extent of patient characteristics used. We were not able to evaluate indirect costs related to SMA. In addition, despite the publication of the ICD-11 by the WHO [16], Poland has not fully introduced the new classification into the reporting system and clinical practice as of May 2023. Therefore, in our research, we reference the commonly used, yet technically outdated, ICD-10 to present the methods utilized in the research and maintain consistency with previous local studies in the field.

5. Conclusions

Poland introduced policy tools that significantly improved the situation of SMA patients in our country—a newborn screening and drug program that grants access to treatment to all patients with a genetic diagnosis of SMA. Extended access to therapy introduced in 2019 successfully reduced patient mortality compared to the situation before the program's introduction.

As of May 2022, 875 patients were treated with disease-modifying therapy. The treated population is likely to expand in time due to new initiatives and reduced patient mortality. The bulk of the costs of the treatment was associated with the cost of the drug, which is covered by a confidential agreement between MoH and MAH. The costs of healthcare benefits granted to patients were stable on a per patient basis, which suggests the

development of standards of care for patients. Our results can be used as a benchmark for resource planning by policymakers in other countries who may consider the introduction of an SMA treatment program and its scope. Further research is warranted to expand on our findings in terms of real-world treatment effectiveness in specific subpopulations and total costs related to SMA treatment, including indirect expenses.

Author Contributions: Conceptualization, D.K. and M.C.; methodology, D.K. and E.C.; validation, D.K., E.C., B.K., M.C., and A.K.-P.; formal analysis, D.K. and E.C.; data curation, D.K. and E.C.; writing—original draft preparation, D.K.; writing—review and editing, D.K. and M.C.; visualization, D.K.; supervision, M.C. and A.K.-P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethical review and approval were waived for this study as it is a retrospective database analysis.

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the analysis and summary result presentation.

Data Availability Statement: Summary information presented herein is available on demand. Due to the patient data confidentiality policy adopted by the NFZ, no information that would enable single patient identification can be shared. This restriction was also applied during the work on this article.

Conflicts of Interest: A.K.-P.—Advisory Board honoraria, lecture honoraria or travel support: Biogen, PTC, Novartis/Avexis, Roche, Investigator in SMA (Roche) clinical trials, institutional grant support by Biogen. M.C.—Advisory Board and lecture honoraria: Biogen. Other authors declare no conflict of interest.

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14.2 Appendix 2: Article 2

Krupa, D., Czech, M., Pinkas, J., & Mosiołek, A. (2022). Impact of COVID-19 Pandemic on the Use of Antidepressant and Antianxiety Pharmaceuticals as Well as Sick Leave in Poland. International Journal of Environmental Research and Public Health (T. 19, Issue 4, s. 2135). MDPI AG. https://doi.org/10.3390/ijerph19042135

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Article

Impact of COVID-19 Pandemic on the Use of Antidepressant and Antianxiety Pharmaceuticals as Well as Sick Leave in Poland

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Abstract: The COVID-19 pandemic caused a major upheaval to the lives of people and placed a strain on societal mental health. The aim of this research is to estimate the impact of the pandemic on the mental condition of the Polish population measured through the consumption of relevant medication and medical leave of absence from the workplace. Methods: We analyzed national-level data on the consumption of pharmaceuticals used in clinical practice in Poland in the treatment of depression and anxiety alongside medical absence in the workplace using the Interrupted Time Series model to estimate the significance of the pandemic. Results: We found no significant change regarding the consumption of pharmaceuticals with the development of the pandemic. Conversely, medical leaves of absence for psychiatric reasons increased significantly with the onset of COVID-19. The influence was strongest in the diagnosis of anxiety or reaction to severe stress and weakest in recurrent depression. Conclusion: The pandemic had a significant influence on the ability to work for psychiatric patients in Poland but did not change pharmaceutical use. Physicians should consider the mental health of patients impacted by the anti-epidemic measures. Further study is needed to fully understand the long-term impact of the pandemic on mental health in Poland.

Keywords: COVID-19; mental health; antidepressants; antianxiety; pharmaceuticals; sick leave; depression; anxiety; Poland

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1. Introduction

The onset of the global pandemic of COVID-19 caused by the novel coronavirus SARS-CoV-2 has caused a major disruption to everyday lives of people everywhere. The first cases were recorded in China in December 2019 and, by March 2020, had spread to most countries around the world, including Poland [1]. A state of epidemic was introduced in Poland on 20 March 2020 and, as of January 2022, was ongoing. Various measures of mobility restrictions and isolation were imposed to prevent exponential spread of the potentially deadly disease [2].

Periods of crisis and uncertainty, such as a global epidemic, are recognized as times of increased incidence of mental disorders in the population [3–5]. Specifically, a connection between mental illness and infectious disease outbreaks, including COVID-19, has also been described in literature [6]. For this reason, the importance of mental health resources for patients in such times has been recognized by researchers [7] as well as the World Health Organization [8].

Nevertheless, there is no official guideline or verification of the effectiveness or availability of mental health support, causing heterogeneity in patient experiences when it

comes to psychiatric support between countries. Moreover, the scale of the impact of the pandemic on the mental health of societies in different geographies remains unknown. While some studies describing the impact of the pandemic on specific groups, including healthcare workers [9], the elderly [10], children [11] or new mothers [12] do emerge, their targeted approach limits the generalizability of the conclusions.

Until large-scale primary studies explicitly evaluating the mental health of populations in the pandemic are published, the question of the scale of the unmet need in psychiatric and psychological state of the population remains open and a burden to policy makers, employers, families and patients. In the meantime, secondary data is a viable source of knowledge that can guide research and decision makers.

Poland is the sixth largest country in the EU, with a population of almost 38 million people. The single payer public healthcare system is one of the lowest funded in the European Union, with 6.5% GDP spent on healthcare, compared to an EU average of 9.9% [13]. Psychiatry specifically is a specific of concern, since according to data from Eurostat, there are only nine psychiatrists for 100,000 inhabitants in Poland [14], a penultimate result in the EU, with only Bulgaria having less.

At the same time, there were 27 psychiatrists in Germany, 18 in Estonia and 15 in Hungary. The relatively low availability of specialists in psychiatry indicates that, in the extraordinary circumstances of a global pandemic, Polish patients may face difficulties in obtaining access to treatment, thus worsening their wellbeing. In this paper, we aim to estimate the impact of COVID-19 on the mental health of the Polish population.

2. Materials and Methods

An analysis of two types of data was conducted. First, we looked at the consumption of antidepressants and antianxiety medication in the population. Secondly, we analyzed the information on the frequency and duration of sick leave due to psychiatric diagnosis.

For the consumption of medication, we analyzed data from IQVIA Pharmascope database on prescription only (Rx) purchases done by patients in community pharmacies. IQVIA Pharmascope is a national-level database containing information on all products purchased in community pharmacies across Poland. Available information for pharmaceuticals includes: pack details (active ingredient, pack size, dose, brand name, manufacturer, EPhMRA Anatomic Therapeutical Classification [15] (ATC) levels 1 through 4), pharmacy identifier, reimbursement status, date of purchase (by month), price of purchase and purchased volume.

We analyzed monthly data from January 2018 until October 2021 for drugs from classes N06A4 SSRI Antidepressants, N06A5 SNRI Antidepressants, N06A9 All Other Antidepressants and one molecule from the N05C0 Tranquillizers class (buspirone). Pharmaceutical consumption data was analyzed in both value and volume, on SKU (Stock Keeping Unit) level as well as the size of therapeutic doses purchased measured through Daily Defined Dose (DDD) for each molecule specified by the World Health Organization [16].

We looked at aggregated trends as well as analysis within the medication subgroups. The database does not contain information on patient characteristics, diagnosis, or the specialty of the physician issuing the prescription, therefore the presented figures will include treatment for multiple disorders as well as potential off-label use of the medication. To limit the effect of potential use in other conditions, verification of molecules used in clinical practice of depression and anxiety management in Poland was conducted by a clinician.

The impact of depression and anxiety on the workforce was analyzed on data on the frequency and duration of medical leave due to a diagnosis of psychiatric condition collected by the Social Insurance Institution of Poland (pol. *Zakład Ubezpieczeń Społecznych*, ZUS). ZUS is a state organizational unit in Poland, whose responsibilities include establishing entitlements to social transfers, collections of social security premiums (retirement, disability, sickness and healthcare) and payment of the benefits, among others [17].

All leaves of absence from the workplace, both short and long-term, must be reported to ZUS. Additionally, justification documentation for the absence for medical reasons must be issued by a physician with the authorization of ZUS and must include information on the diagnosis that is the direct cause of inability to work. For this research, we procured data on medical absence due to selected ICD10 diagnoses: F32—depressive episode; F33—recurrent depressive disorder; F41—other anxiety disorder; and F43—reaction to severe stress and adjustment disorders; spanning the period of January 2018 to April 2021. The scope of the data included the count of patients and average duration of sick leave.

Both types of collected data included a period before the onset of the pandemic, and several months of its duration in Poland. To compliment and contextualize the two primary datasets, additional sources were used. Data on the population of patients dealing with depression and/or anxiety in Poland were sourced from the National Health Fund publications and from the results of a large epidemiological study on mental illness in Poland—the EZOP project [18]. Data on the development of the pandemic in Poland for incidence, COVID and non-COVID-related mortality, as well as restriction stringency was sourced from OurWorldInData [1], an open-source database updated daily. For this paper, daily data for the period 1 January 2020 until 1 December 2021 was analyzed.

Interrupted Time Series analysis was used to validate impact of the onset of COVID pandemic on pharmaceutical consumption and number of issued sick leave notes. To estimate the significance of COVID-19 on the analyzed series, we used two synthetic variables—a dummy for the period of the duration of the pandemic (from March 2020 to October2021) and a linear trend in the same period to capture slope change.

Statistical analyses were conducted in the open-source software R, version x64 4.1.2 [19], using the RStudio interface. Data visualizations were done in MS Excel version 2102 (Microsoft Corporation, Redmond, WA, USA).

3. Results

The estimated prevalence of depression in adults in Poland was estimated at 3.17% in the Global Burden of Disease Study [20] for the general population, and at 3.85% in the results of the latest nation-wide epidemiological study EZOP II for adults [21]. This corresponds to a population estimate between 1.2–1.45 million. Simultaneously, the lifetime prevalence of anxiety attacks is estimated at 7% in the EZOP II study, equivalent to 1.3% annually. The authors estimate that there are around 2.2 million people who have suffered from anxiety in Poland. Data from the NFZ report that reimbursement for antidepressants and antianxiety medication has been granted to 1.38 million people in 2020 [22].

3.1. Drug Consumption

The overall Rx market in pharmacies was worth 4.4 billion EUR [23]. The antidepressant and antianxiety medications that are the focus of this study constitute approximately 2.6% of the total Rx market value. According to data from IQVIA Pharmascope, annually, patients in Poland purchased more than 20 million packs of antidepressants and antianxiety medication valued at more than 114 million EUR. The monthly consumption of pharmaceuticals in this category in 2021 amounted to 2.3 million packs for the cumulative value of 12 million EUR.

The consumption of pharmaceuticals indicated for treating depression and anxiety has been increasing steadily in Poland over the last years. The monthly consumption of antidepressants and antianxiety medication between January 2018 and October 2021 increased from almost 40 million doses to almost 60 million. The increase follows a linear trend as presented in Figure 1.

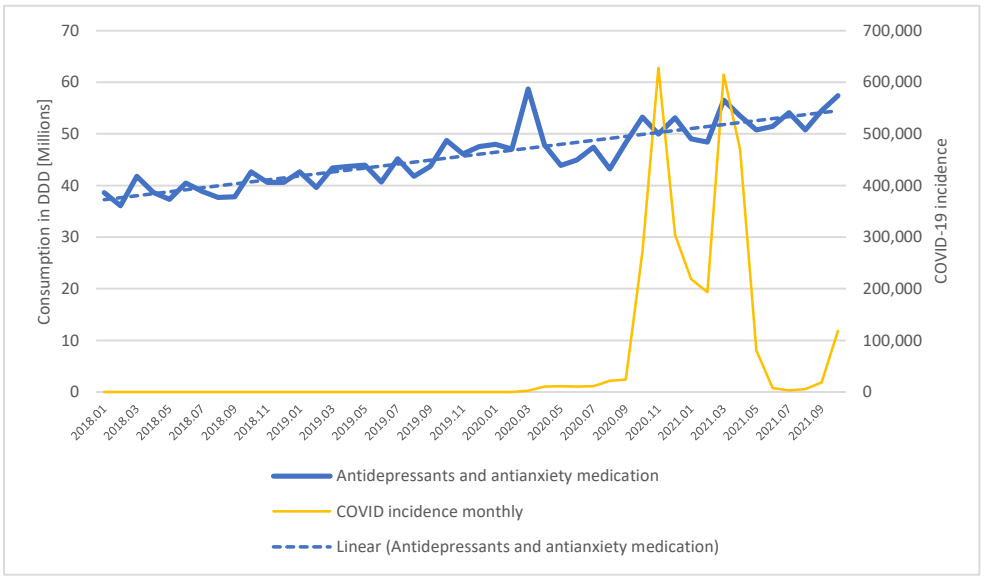

Figure 1. Consumption of all antidepressants and antianxiety medication in Poland in DDD, January 2018–October 2021.

A peak in purchases was recorded in March 2020 with the onset of pandemic in Poland, followed by slightly lower sales over the next 6 months and ultimately returned to the previous dynamics.

Development of specific categories is presented in Figure 2. The most popular products are Selective Serotonin Reuptake Inhibitors (SSRI), representing 64% of the entire volume, followed by antidepressants of other mechanisms with 21% of volume and Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) with 14.5%. Buspirone molecule classified as tranquilizer covers 0.3% of volume. All categories of medication present similar development patterns in time, with SNRI growing at a slightly larger rate. Consistency in growth path is confirmed by high Pearson correlation factors along with significance levels at $p < 0.01$, as presented in Table 1.

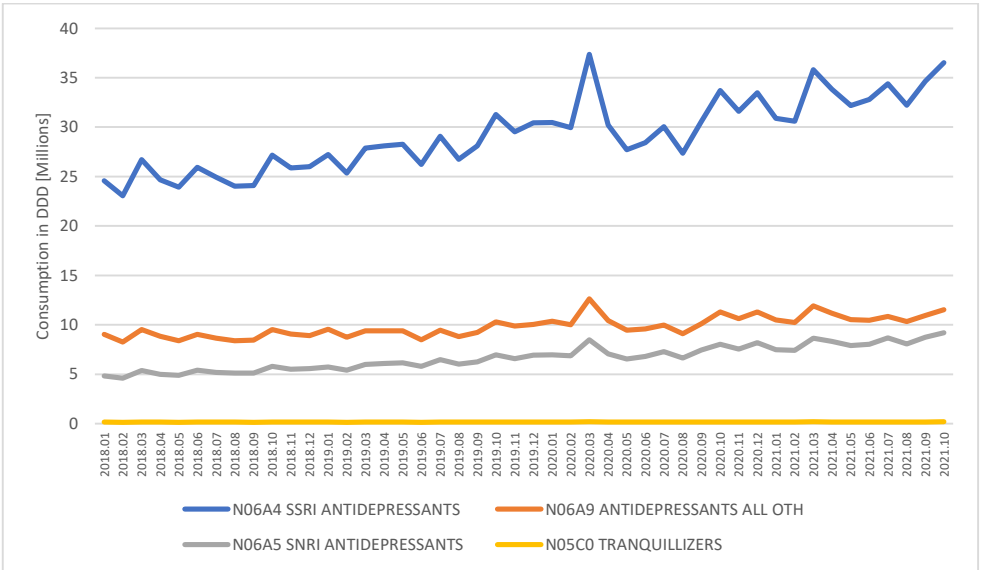

Figure 2. The consumption of antidepressants and antianxiety medication in Poland by ATC4 classification, January 2018–October 2021.

Table 1. Correlation matrix between drug classes in the period January 2018–October 2021.

	N06A4 SSRI	N06A9 OTHER	N06A5 SNRI	N05C0 TRANQUILLIZERS
N06A4 SSRI	1.00			
N06A9 OTHER	0.97 ***	1.00		
N06A5 SNRI	0.98 ***	0.92 ***	1.00	
N05C0 TRANQUILLIZERS	0.95 ***	0.96 ***	0.91 ***	1.00

Note: *** $p < 0.01$. N06A4 SSRI—Selective Serotonin Reuptake Inhibitors; N06A5 SNRI—Serotonin-Norepinephrine Reuptake Inhibitors; N06A9 OTHER—all other antidepressants not classified elsewhere.

Within the analyzed classes, the ten most popular molecules account for 91% of dose volume sales. Out of the ten, seven molecules are reimbursed and available in community pharmacies in Poland. For each molecule, the pack with the highest sales volume was selected to present the cost for the patient. The pack price for the most popular drugs ranges from 3.86 to 6.05 EUR. When purchased with reimbursement, the co-payment ranges from 0.75 to 2.44 EUR per pack. Table 2 presents the key characteristics of the most popular molecules in relevant therapy in Poland.

Between January 2018 and October 2021, the consumption of antidepressants and antianxiety medication in DDD grew by 48.8%. New products introduced into the market in that time accounted for 5.9% of growth. Previously available products pack volume increased by 27.7%. The average size of pack increased by 4.3%, while the average dose per tablet increased by 5.4%.

Since the data does not include information on the number of patients on therapy, it is not possible to precisely estimate the magnitude of the increase in patient population, since it is not known how many of the additional packs or new products were purchased by patients previously treated and how many were purchased as initiation within that period. However, an increase in pack size or in dose could have been purchased only by the same patient and, therefore, can be interpreted as therapy intensification. In the analyzed period, on average, the dose of medication increased by 10.0%, as patients purchased larger packs with higher doses per tablet.

Interrupted time series analysis of the drug consumption included three variables—underlying linear trend (denoted as Period), a dummy variable for the duration of the COVID pandemic (COVID fixed) and a linear trend from the onset of COVID-19 (COVID variable). The results of the regression are presented in Table 3. Neither COVID variable achieved statistical significance, confirming that no trend break occurred within the analyzed period, and the pandemic did not have a significant impact on the consumption of antidepressant and antianxiety medication in Poland in terms of volume.

3.2. Sick Leave

Before the pandemic there were roughly 70,000 sick leave notes issued for the diagnoses related to depression and anxiety in Poland monthly. Between January 2018 and January 2020, the number has been increasing at a pace of 0.44% monthly. When the pandemic started in March 2020, the number of sick notes grew to 107,000 in March 2020 and reached a peak in April 2020 at 132,000. Dynamics by specific diagnoses are presented in Figure 3. The intensive period of increased sick leave issuance lasted for about six months until August 2020 and later stabilized. However, some lasting effects are visible, as the level of notes prescribed for F43 visibly did not return to levels from before the pandemic.

Table 2. Most popular antidepressant and antianxiety medication in Poland, 2021.

Molecule	ATC4 Category	Reimbursement Status in Poland [September 2021]	DDD [mg]	Most Popular Pack	DDD Consumed 2021 (January–October), Millions	Share of DDD Consumption in 2021 (January–October), %	2021 Market Value (January–October), Million EUR	2021 Market Volume (January–October), Million Packs	Average Pack Price, EUR	Average Co-Payment to Most Popular Pack [September 2021], EUR
SERTRALINE	N06A4 SSRI ANTIDEPRESSANTS	Yes	50	50 mg 30 tabs	133.01	25%	13.73	3.56	3.86	0.92
ESCITALOPRAM	N06A4 SSRI ANTIDEPRESSANTS	No	10	10 mg 28 tabs	82.88	16%	13.59	2.76	4.91	n/a
VENLAFAXINE	N06A5 SNRI ANTIDEPRESSANTS	Yes	100	75 mg 28 caps, extended release	58.64	11%	13.24	2.34	5.67	1.67
FLUOXETINE	N06A4 SSRI ANTIDEPRESSANTS	Yes	20	20 mg 30 tabs	40.11	8%	6.33	1.33	4.76	1.78
CITALOPRAM	N06A4 SSRI ANTIDEPRESSANTS	No	20	20 mg 28 tabs	38.68	7%	5.95	1.28	4.64	n/a
PAROXETINE	N06A4 SSRI ANTIDEPRESSANTS	Yes	20	20 mg 30 tabs	36.73	7%	4.89	1.10	4.43	1.64
OPIPRAMOL	N06A9 ANTIDEPRESSANTS ALL OTH	No	150	50 mg 56 tabs	26.60	5%	11.19	1.89	5.93	n/a
TRAZODONE	N06A9 ANTIDEPRESSANTS ALL OTH	Yes	300	75 mg 30 tabs, extended release	26.35	5%	12.18	2.13	5.72	2.44
DULOXETINE	N06A5 SNRI ANTIDEPRESSANTS	Yes	60	30 mg 28 caps	23.79	5%	5.93	0.98	6.05	1.39
MIANSERIN	N06A9 ANTIDEPRESSANTS ALL OTH	Yes	60	10 mg 30 tabs	13.37	3%	5.33	1.29	4.14	0.75

Note: XR—extended release. DDD—Defined Daily Dose.

Table 3. Interrupted time series analysis of drug consumption.

	Consumption		
Predictors	**Estimates**	**CI**	***p***
(Intercept)	36,656,603	34,342,014–38,971,192	<0.001
Period	398,673	248,797.8–548,548.2	<0.001
COVID fixed	137,746	−3,306,424–3,581,916	0.938
COVID variable	−47,282	−315,355–220,791.8	0.732
Observations		46	
R2/R2 adjusted		0.768/0.752	
F Statistic (df = 3; 42)	46.466		<0.001

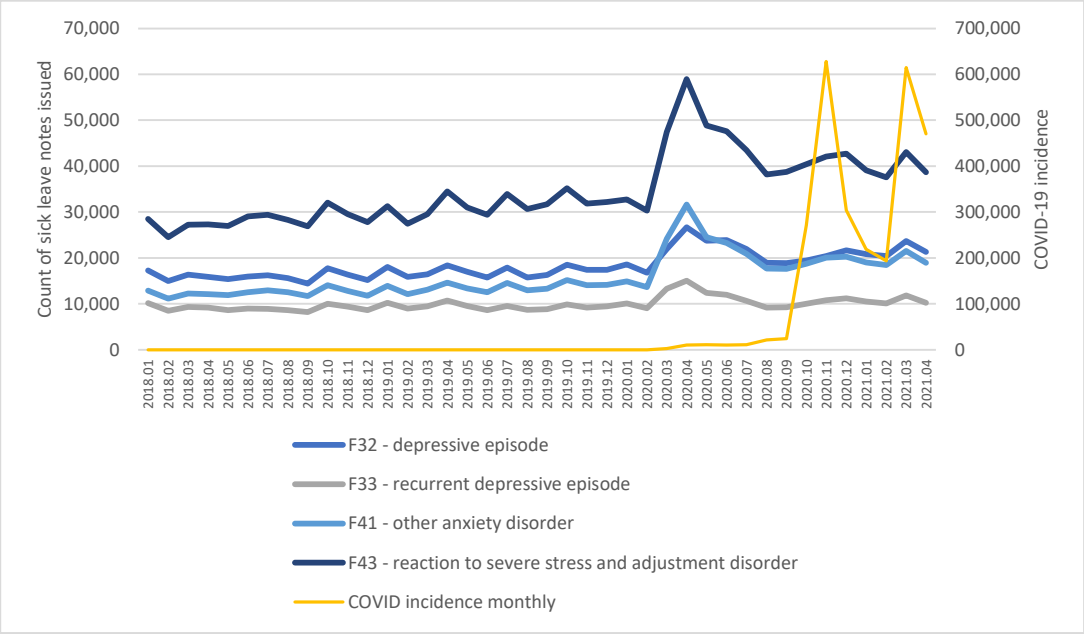

Figure 3. Count of sick leave notes issued in Poland, January 2018–April 2021.

Interrupted time series analysis further confirmed the conclusion that COVID had a significant influence on the number of sick leave notes. Detailed results of the regression are presented in Table 4. Out of the four analyzed diagnoses, before the onset of the pandemic only F43 was characterized by a significant upward trend ($p < 0.01$). However, for each of the diagnoses, the COVID fixed dummy variable had a significant positive influence on the number of sick leave notes issued ($p < 0.001$). The strongest relative effect was observed for F41 diagnosis and the weakest for F33, recurrent depressive episodes. Linear trend associated with COVID was also significant for each diagnosis and was negative, indicating a decreasing impact of the pandemic over time.

Table 4. Regression results on the impact of COVID-19 on number of sick leave notes issued for diagnoses of anxiety and depression.

	Model											
	F32—Depressive Episode			**F33—Recurrent Depressive Episode**			**F41—Other Anxiety Disorder**			**F43—Reaction to Severe Stress and Adjustment Disorder**		
Predictors	**Estimates**	**CI**	***p***	**Estimates**	**CI**	***p***	**Estimates**	**CI**	***p***	**Estimates**	**CI**	***p***
(Intercept)	15,588.43	14,370.79–16,806.08	<0.001	9070.65	8286.10–9855.21	<0.001	11,804.04	10,276.14–13,331.94	<0.001	26,640.07	24,242.09–29,038.04	<0.001
Period	74.63	−4.21–153.48	0.063	15.13	−35.67–65.94	0.55	97.43	−1.51–196.36	0.053	247.29	92.02–402.57	0.003
COVID fixed	5621.17	3567.29–7675.04	<0.001	3328.46	2005.10–4651.81	<0.001	11,139.07	8561.88–13,716.27	<0.001	17,555.04	13,510.23–21,599.85	<0.001
COVID variable	−268.42	−483.32–−53.52	0.016	−230.90	−369.36–−92.44	0.002	−667.22	−936.87–−397.57	<0.001	−1216.00	−1639.21–−792.79	<0.001
Observations		40			40			40			40	
R2/R2 adjusted		0.761/0.741			0.570/0.534			0.845/0.832			0.862/0.851	
F Statistic (df = 3; 36)		38.22	<0.001		15.894	<0.001		65.354	<0.001		75.132	<0.001

4. Discussion

The data on pharmaceutical drug consumption and medical leaves of absence indicates that the impact of COVID-19 pandemic had mixed effects on patients suffering from depression or anxiety in Poland. On one hand, medical absence associated with diagnosis of anxiety or depression increased significantly with the onset of restrictions aimed at combatting the pandemic. This suggests either that patients observed worsening of their condition or that the population increased. On the other hand, pharmaceutical consumption growth does not mirror this behavior, having increased in the initial month only slightly before returning to the long-term dynamics.

On its own, the lack of significant increase in consumption associated with COVID-19 stands in contrary to data from the UK [24], where researchers found a significant surge in pharmaceutical use in the pandemic. In Germany [25], a decrease in the prescription of drugs for mental disorders was identified. Interestingly, similarly to this study, research from Portugal found no impact of the pandemic on the increasing prescribing trends of drugs of interest [26].

The hypothesis for the disparity could therefore be that patients suffering from depression and anxiety (in Poland) did not fare worse when faced with the new reality—or, alternatively, it indicates that a potentially large population of patients should be undergoing pharmacotherapy but are not, either due to a lack of awareness, unwillingness to try, poor compliance or limited access to psychiatric care, putting them at higher risk of adverse events associated with depression and anxiety. It is, however, also possible that the data used in this study does not accurately capture the impact of the pandemic on the consumption of prescription medication. This would indicate a potentially large population of patients at higher risk of adverse events associated with depression and anxiety [27].

The hypothesis of underdiagnosis of depression in Poland can be strengthened by information presented within the Global Burden of Disease study [20], where the depression and anxiety rates per 10,000 population in Poland in 2019 were estimated at 2.836 (14% lower than Central European countries (Countries in Central Europe as defined by the Institute of Health Metrics and Evaluation are: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Montenegro, North Macedonia, Poland, Romania, Serbia, Slovakia and Slovenia)) and 3.489 (6% lower than the region) respectively.

The argument for underdiagnosis of those mental conditions in Poland is stronger, since while, historically and socially, the countries have many similarities, Poland is one of the better developed economically, suggesting potentially better access to healthcare services. Globally, the use of antidepressants and antianxiety medication is growing, particularly in high income countries [28].

Between 2008 and 2019, the average consumption per day per 1000 inhabitants in high income countries measured by daily defined dose increased from 51.98 to 72.93, indicating a 40% increase and equivalent to an average compound growth of 3% per year [28]. According to the data obtained for this study, in January 2018, the DDD consumption for 1000 citizens per day was 32.94 doses; whereas, in October 2021, it was 49.01, representing a 49% increase over a little under three years, rather than 12 years.

This suggests that consumption of antidepressants and antianxiety medication in Poland vastly outpaces the developed world. Nevertheless, the levels remain below the average consumption in high income countries in 2008, showing the level of the gap still to be breached to improve the care of patients suffering from depression or anxiety in Poland.

Alternatively, the patients may not have had access to doctors who would be able to issue a prescription. This hypothesis is however disproven by the increase in sick leave notes, which must be issued by doctors. Therefore, it is possible that the patients who obtained medical leave privileges are not undergoing treatment for their mental health problems. This could explain some increase in sick leave notes issued, as it is possible that workers in unsteady employment were afraid of losing their job under the unpredictable circumstances brought around by COVID-19. The relatively low cost of pharmacotherapy,

with monthly cost starting at 0.75 EUR per month of therapy, indicates that economic barriers are not the primary limiting factor for treatment.

Verification of those hypotheses warrants further study whenever new data becomes available, as they carry important implications to health policy.

This study has several limitations. As the pandemic was ongoing as this research was being published, it was impossible to assess the full impact of COVID-19 on mental health in Polish patients. Secondly, the data obtained enables analysis on a level of aggregation which may obstruct the detection of underlying granular trends. Thirdly, the low number of observations in the analyzed time series inflates the uncertainty in estimates by reducing the scope for more sophisticated numerical analysis. The monthly format of the data inhibits the use of more time-sensitive variables, such as governmental restrictions, whose impact on drug consumption or sick leave would need to be quantified using higher granularity observations.

5. Conclusions

Although the COVID-19 pandemic had a significant impact on the frequency and duration of sick leaves due to depression or anxiety in Poland, the consumption of pharmaceuticals remained largely unaffected and has been increasing at a consistent rate since 2018. Further study is needed to fully understand the reasons behind this and to determine whether the cause lies in consistently insufficient awareness of treatment in the population, restricted access to psychiatric care or alternative methods of coping with depression prevalent within the Polish population.

This study showed that the COVID-19 pandemic may have a significant impact on mental health. Physicians should pay attention to the mental health problems among patients who were affected by the anti-epidemic measures, such as lock-down and remote work. Moreover, public health programs are needed to address the growing burden of mental health illnesses.

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14.3 Appendix 3: Article 3

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The Potential to Reduce Patient Co-Payment and the Public Payer Spending in Poland through an Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by the Real-World Big Data Analysis

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Abstract: High medication costs are one of the major barriers to patient adherence. Medication affordability might be improved by generic substitution. The aim of this study was to assess the effectiveness of the implementation of generic substitution mechanisms in Poland. This was a retrospective analysis of nationwide real-world big data corresponding to dispensation of metformin preparations in 2019 in Poland. Relevant prescription and dispensation data were compared to assess the prevalence of generic substitution and its economic consequences. Among the 1,135,863 e-prescriptions analysed, a generic substitution was found in only 4.81% of the packs dispensed, based on e-prescriptions issued for metformin under its originator version and 2.73% under generic drugs. It is estimated that if these values were applied to the total Polish drug market, patients could lose the opportunity to lower their co-payment by 15.91% and the national payer to reduce its reimbursement expenditures by 8.31%. Our results point at the suboptimal implementation of generic substitution in Poland. Therefore, relevant actions need to be taken in order to maximise the benefits provided by this mechanism. It could not only lead to the win-win scenario in which both patients and the national payer are secured substantial savings, but it could also have a positive impact on patient adherence.

Keywords: generic substitution; generic drugs; drug costs; adherence; pharmacoepidemiology; Poland; retrospective studies; real-world data; big data

1. Introduction

Securing patient adherence to long-term therapies is one of the major challenges faced by modern public health. In its seminal report published in 2003, the WHO indicated that the level of non-adherence reached 50% in chronic treatments [1]. Although nearly two decades have passed, not much of an improvement may be observed in this field. New studies prove that non-adherence is still equally prevalent. For example, a recent meta-analysis found the prevalence of non-adherence to antihypertensive medications in Asia to be 48% [2]

As with all complex behaviours, non-adherence may have diverse underlying causative factors. The WHO model distinguishes five clusters of such drivers. Along with the patient, condition, medication, and healthcare system-related determinants, these are also

social and economic factors which profoundly influence medication adherence [1]. Among these factors, drug costs play a very important role [3]. Higher out-of-pocket costs for patients have consistently been associated with various forms of non-adherence, including non-initiation, poor implementation (e.g., skipping or reducing doses), and early discontinuation of long-term therapies (poor persistence) [4].

Unfortunately, drug costs tend to grow, challenging the sustainability of public healthcare systems and creating serious obstacles to adherence. In such a case, at least a partial solution of this problem could be provided by a wider use of generic drugs. Current evidence supports this point, proving that more expensive drugs might be safely replaced by their more affordable generic equivalents [5].

In order to stimulate a wider use of generics, many countries allow for a mechanism of generic substitution. According to WHO, generic substitution is the practice of replacing a medicine, whether marketed under a trade or generic name, with a lower-priced alternative medicine (a branded or unbranded generic) [6]. Generic substitution is a widely used tool in the drug policy of healthcare systems. It secures higher savings for the healthcare system, intensifies competition between manufacturers, and increases the availability of treatment for patients. Particularly, it is the last of the mentioned advantages that plays an important role for many vulnerable groups, such as those suffering from multiple chronic conditions or the elderly, who often struggle with the overall burden of healthcare costs.

For several European markets (Denmark, Finland, Greece, Spain, Netherlands, Ireland, Portugal, and Sweden), generic substitution is mandatory, while for others, it is just recommended (France, Norway, and Switzerland) [7]. Generic substitution was included in the official Drug Policy 2018–2020, a strategic document issued by the Polish government [8], in accordance with the WHO guidance, which advocated the use of generics to contain expenditure [9].

However, by providing more affordable therapies, generic substitution can offer benefits that go beyond cost containment. Most studies evaluating the use of generic (rather than brand-name) drugs, applied in the treatment of chronic diseases, show a significantly higher long-term adherence following treatment initiation [10]. For example, adherence to generic, versus brand-name, statins has been extensively studied. Recent studies proved adherence and persistence to be higher among generic statin recipients in Sweden [11] and Japan [12]. As compared to those initiating brand-name statins, patients initiating generic statins in the USA were more likely to adhere and had a lower rate of a composite clinical outcome (comprising of hospitalization for an acute coronary syndrome or stroke and all-cause mortality) [13]. Similar observations were made in other scenarios, e.g., among elderly patients receiving antidiabetics, in whom the substitution between branded and unbranded products (as well as between generics) of the same substance did not negatively affect adherence, not even in multiple switchers [14]. In French patients initiating bisphosphonates, the prescribing of a generic drug led to a higher persistence rate and to better implementation at 1 year [15]. Generic initiation was also associated with improved adherence to antidepressants, [16], aromatase inhibitors [17], and imatinib [18].

Thus, a wider use of generic drugs seems to be reasonable, both from the perspective of the healthcare system (because of cost containment), as well as from the patient's perspective, as an enabler of medication adherence and its positive clinical and economic consequences. There is evidence proving that a higher adherence is associated with a lower risk of hospitalisation and lower overall health care costs related to chronic conditions [19]. Thus, a greater use of generic therapies can reduce overall healthcare system expenditure, both directly and indirectly.

Among European countries, Poland was found to have higher rates of non-adherence. In a cross-European study assessing adherence to antihypertensive treatment, the average level of non-adherence was 44%, whereas in Poland this value was much higher, i.e., 58% [20]. Another study found non-adherence in Poland as high as 83.8% in selected

chronic conditions [21]. Thus, the implementation of medication adherence-enhancing interventions (in particular, an effective use of generic substitution) is extremely important in Poland.

The Polish healthcare system, like many other European systems, is a health insurance system based on the principle of social solidarity. Health services are provided free of charge to those insured (i.e., practically the whole population) by both public and private healthcare providers, and their costs are covered by the only national health payer, i.e., the National Health Fund (NHF). The NHF also provides reimbursement for prescribed drugs. Nevertheless, most drugs are subject to an out-of-pocket co-payment by patients, which varies across and within drug classes. Several drugs of crucial importance for particular therapies are available at a lump sum of PLN 3.20 (PLN—Polish zloty; approximately PLN 4.50 = EUR 1, as of June 2021), and some are free of charge. In the case of other medicines, patients pay 30%, 50%, or 100% of total drug costs out-of-pocket, depending on the effectiveness of the drug, according to evidence-based criteria (e.g., homeopathic drugs are paid 100%). The co-payment is organized around the idea of stimulating the use of generic drugs, as a result of the adoption of the reference price system, based on ATC classes 5, 4, and 3. This system categorizes medicines that are considered interchangeable (e.g., an originator and its generic equivalents) into one cluster, enabling the public payer to cover the same reimbursement amount for all medicines included in that cluster. Consequently, originator drugs generate higher co-payments than generics. In these conditions, patients are financially incentivized to use generics, in order to lower their co-payments [6]. In order to optimize the cost of therapy to the patient, improve adherence, and generate savings for the public payer, current Polish legislation establishing the rules of the dispensation of reimbursed products in community pharmacies [22] makes it obligatory for pharmacists and technicians to offer a less expensive alternative, with an equivalent formulation, to patients filling a prescription for a reimbursed product.

The effectiveness of the practical implementation of generic substitution has not been thoroughly studied in Poland yet. Considering the present high levels of co-payments for pharmacotherapy in Poland (reaching, on average, more than 60% of an original drug price in 2017) [23], it may be assumed that the full potential of generic substitution has not been reached. In this study, we hypothesized that currently, the mechanism of generic substitution is underused in Poland, leading to increased patient co-payments and public payer spending. Therefore, the overall aim of this study was to assess, based on real-world data for the general population, how effectively generic substitution is used in Poland, and to what extent this substitution can be optimised to increase the affordability of the drugs for patients. The study also analysed whether this potential optimisation could generate additional savings, rather than costs, for the national payer organisation (NHF). The analysis was possible only recently, due to the introduction of e-prescriptions, which, after being piloted in 2018, came into regular use in Poland in 2019. It was the first time that the data on issued prescriptions had been collected on a mass scale, as well as analysed and compared to the data on filled prescriptions.

2. Materials and Methods

2.1. Data and Study Design

This was a retrospective, custom-made analysis of the 2019 anonymised drug prescription and dispensation data possessed by NHF. In our study, we adopted metformin as a model drug, which is widely used in diabetes care. The medication is not only available in Poland, in both a generic and an originator form, but it also plays a significant role in both patients' co-payments and NHF's reimbursement expenditures (in 2019, it accounted for 3.27% of the total patient co-payment, and 2.03% of the total NHF reimbursement budget, being number two on the NHF reimbursement list of drugs incurring the highest expenditures) [24].

The NHF database registers full information on prescription drugs dispensed in community pharmacies in Poland, regardless of whether a particular prescription was issued by a public or a private healthcare provider. This data includes the quality and quantity of the medicinal products dispensed, as well as the economic data (such as the cost of a particular drug), details on patient co-payments, and the reimbursement costs incurred by the NHF.

The prescription data came from e-prescriptions. After the pilot program was introduced in 2018, e-prescriptions started to be widely used in Poland in 2019, covering a large part of prescriptions. This allowed for the collection of the original data that was entered by practitioners on prescriptions when issuing them. The use of unique identifiers allowed the merging of original prescription and dispensation data in each individual case. Thus, it was possible to compare the medicinal products prescribed and dispensed, as well as to trace all the steps of generic substitution.

Reimbursement and co-payment levels in Poland have changed over the time. In 2019, the reimbursement lists were amended six times. Following standard procedures, the currently binding reimbursement list has been used to calculate reimbursement as per the date of dispensation. A similar procedure has been used to calculate reimbursement as per the date of prescribing. It is noteworthy that due to the evolution of the national reimbursement lists, relevant values for the same medicinal product, as per prescribing and dispensation, may differ.

In this analysis, only single-compound drugs containing metformin (i.e., the ones matching the Anatomical Therapeutic Chemical (ATC) code of A10BA02) were analysed. Consequently, multi-compound drugs were not analysed.

Various presentations of Glucophage (Merck Sante s.a.s., Lyon, France) were collectively counted as the 'originator drug', whereas all the other drugs containing metformin were collectively counted as 'generic drugs'. In order to be considered an equivalent, a medicinal product was required to have the same strength and formulation (e.g., an immediate-release dosage or a modified-release dosage).

For the calculation of the volume of the total metformin market in Poland, we used the national dispensation data recorded in the NHF database. For the assessment of the generic substitution, only e-prescription data could be used. These represented approximately 10% of all prescriptions issued for metformin, as the remaining 90% were issued in traditional paper-based form, not allowing for the analysis of the drugs prescribed.

From a total number of 1,539,863 e-prescriptions issued in Poland for various metformin preparations in 2019, we excluded those which, for various reasons, were not reimbursed, and those which were not dispensed. In order to reflect the actual level of reimbursement and patient co-payment, we also excluded prescriptions dispensed with incorrect reimbursement applied. Thus, the final analysis included 1,135,863 e-prescriptions (see Figure 1 for details of the e-prescription selection).

2.2. Ethics

Analyses of aggregated, anonymised prescription and dispensation data does not involve ethical issues. Therefore, according to the policy of the Ethical Commission of the Medical University of Lodz, this analysis was not subject to the ethical approval procedure.

2.3. Statistical Analyses

In descriptive statistics, both the original numbers and percentage rates, calculated out of the total number of identified substitution cases, were presented, unless otherwise stated. Values were compared with relevant tests with a p-value of less than 0.05 considered significant.

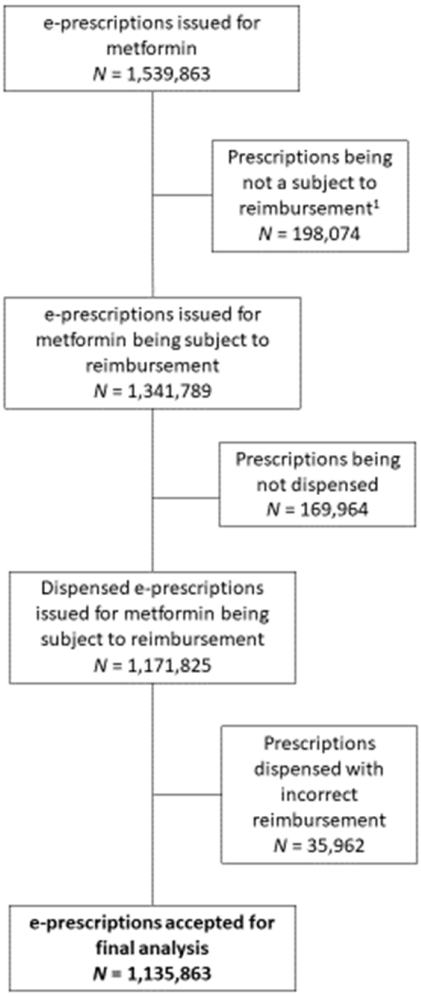


Figure 1. Flow chart presenting a selection of e-prescriptions issued for metformin in Poland in 2019 to be included in the final analysis; (1) e-prescriptions issued to citizens who did not benefit from reimbursement, e.g., those not covered by NHF insurance, foreigners, etc.

3. Results

3.1. National Metformin Market

Details on the total metformin market in Poland in 2019 are presented in Table 1. According to this data, 10,973,123 prescriptions for metformin preparations were dispensed in Poland, based on which patients were dispensed 19,580,846 packs of various medicinal products containing metformin. As many as 74.55% of these prescriptions led to the dispensation of generic drugs, which altogether accounted for 70.06% of the total number of packs of the various medicinal products containing metformin being dispensed.

The total cost of the dispensed metformin was 298,633,242 PLN, of which 192,183,292 (64.35%) was subject to reimbursements, whereas 106,449,949 (35.65%) was covered by patients as the out-of-pocket co-payments. The share of the generic drugs was 66.73% in total costs, 76.13% in reimbursements, and 49.78% in co-payments. On average, the cost of one single-pack of dispensed generic metformin was 14.53 PLN, out of which patients paid 3.86 PLN on an out-of-pocket basis (26.59% of the original total price). The cost of one pack of the dispensed originator drug was 16.94 PLN on average, out of which the

out-of-pocket co-payment made by patients amounted to 9.12 PLN (53.82% of the original total price).

Table 1. Metformin market in Poland in 2019; data refer to the dispensation period between 1 January–31 December 2019; # numbers and percentages do not sum up to the total, as some prescriptions being issued for more than one pack of drug were dispensed in a form of both a generic and the originator drug. NHF: National Health Fund. PLN: Polish zlotys.

Drug	Prescriptions #		Packs		Total Drug Costs		Reimbursement Incurred by NHF		Patient Co-Payment	
	N	%	*N*	%	PLN	%	PLN	%	PLN	%
Generics	8,180,452	74.55	13,717,759	70.06	199,289,203	66.73	146,303,153	76.13	52,986,049	49.78
Originator	2,881,556	26.26	5,863,087	29.94	99,344,039	33.27	45,880,139	23.87	53,463,900	50.22
Total	10,973,123	100.00	19,580,846	100.00	298,633,242	100.00	192,183,292	100.00	106,449,949	100.00

3.2. Generic Substitution

The analysed group of e-prescriptions ultimately included 1,135,863 prescriptions for various metformin formulations (see Figure 1). Out of this number, only 4.08% (46,295) were dispensed with substitution. For packs dispensed, the relevant percentage was even lower, i.e., 3.36% (70,064 out of a total of 2,085,954, see Table 2). Among specific age groups, substitution occurred most frequently among patients aged 18–29 years (4.11% out of the total number of packs dispensed in this age group, $p < 0.01$). The percentage of drug packs dispensed with substitution was very similar across genders (females: 3.38%, males: 3.33%, $p > 0.05$). Finally, there was a significant difference in the percentages of drug packs dispensed with substitution between drugs originally prescribed as the originator and a generic drug (4.81% vs. 2.73%, $p < 0.01$), although both those numbers were low.

Table 2. The analysis of dispensation of metformin e-prescriptions issued in Poland in 2019 (data refer to the dispensation period between 1 January–31 December 2019); # other forms of dispensation which do not satisfy the definition of generic substitution, such as dispensation of a pack with a dosage or a number of units other than those prescribed, other formulation (e.g., an immediate-release formulation instead of a modified-release one), etc.

Variable		Dispensed without Generic Substitution		Dispensed with Generic Substitution		Other #		Total
		Number of Packs Dispensed	%	Number of Packs Dispensed	%	Number of Packs Dispensed	%	
Age	0–17	1621	85.36	64	3.37	214	11.27	1899
	18–29	10,992	82.04	551	4.11	1855	13.85	13,398
	30–49	117,348	82.31	5627	3.95	19,596	13.74	142,571
	50–69	831,280	83.60	35,275	3.55	127,800	12.85	994,356
	70–89	742,650	81.62	27,753	3.05	139,449	15.33	909,853
	90+	19,241	80.58	794	3.33	3843	16.09	23,878
Gender	Female	951,449	82.41	39,050	3.38	164,022	14.21	1,154,520
	Male	771,685	82.85	31,014	3.33	128,735	13.82	931,434
Drug prescribed	Generic	1,202,735	82.45	39,881	2.73	216,175	14.82	1,458,792
	Originator	520,398	82.98	30,183	4.81	76,581	12.21	627,162
Total		1,723,133	82.61	70,064	3.36	292,757	14.03	2,085,954

3.3. Economic Consequences of Generic Substitution

Dispensation of metformin e-prescriptions, issued with and without substitution, was analysed in terms of its economic consequences (Table 3). Dispensation with generic substitution enabled the patient to save, on average, PLN 0.99 per pack of a metformin preparation. This amount could be nearly doubled, reaching PLN 1.78, if the substitution was optimised, i.e., if in each case the preparation with the lowest possible co-payment level was dispensed, respectively. Interestingly, substitution also ensured savings to the payer since, as a result of the substitution, the NHF paid, on average, PLN 0.28 less for

reimbursement of one pack of a metformin preparation. Here again, the optimisation of reimbursements could increase NHF savings (in fact, tripling it (increasing the amount to PLN 0.94)).

Dispensation without generic substitution resulted in lost savings for both the patient and NHF (on average, PLN 1.04, and PLN 1.18, respectively, per one pack of a metformin preparation dispensed).

Table 3. Economic consequences of dispensing e-prescriptions for metformin preparations with and without generic substitution in Poland in 2019 (data refer to the dispensation period between 1 January–31 December 2019); # non-zero values resulting from the change of the reimbursement level between the date of prescribing and dispensation; NHF—National Health Fund; PLN—Polish zlotys.

		Dispensed with Generic Substitution		**Dispensed without Generic Substitution**	
		Total Savings (PLN)	**Average Savings per 1 Pack Dispensed (*N* = 70,064)**	**Total Savings (PLN)**	**Average Savings per 1 Pack Dispensed (*N* = 1,723,133)**
Patient	Real savings (co-payment as per prescription—co-payment paid)	**69,640**	**0.99**	**−1025 #**	**0.00**
	Maximal potential saving (co-payment as per prescription—minimal co-payment)	**124,797**	**1.78**	**1,799,870**	**1.04**
	Lost saving (co-payment paid—minimal co-payment)	**55,633**	**0.79**	**1,800,895**	**1.04**
NHF	Real savings (reimbursement as per prescription—reimbursement incurred)	**19,743**	**0.28**	**1267 #**	**0.00**
	Maximal potential saving (reimbursement as per prescription—minimal reimbursement)	**65,821**	**0.94**	**2,028,644**	**1.18**
	Lost saving (reimbursement paid—minimal reimbursement)	46,324	0.66	2,027,465	1.18

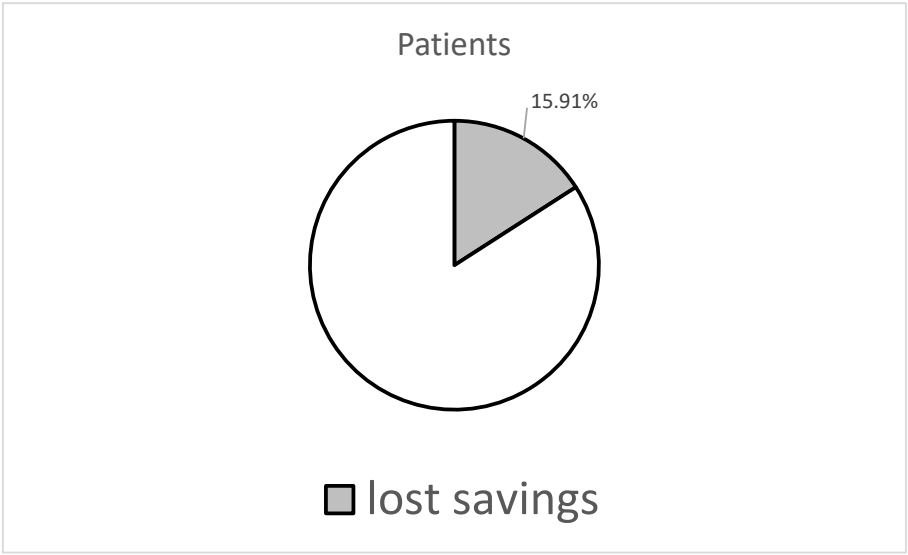
3.4. Lost Savings Due to Suboptimal Generic Substitution

We used the values of the lost savings to calculate the total loss for both patients and the NHF in Poland in 2019, due to dispensation of various metformin preparations without economic optimisation, i.e., savings that would be potentially possible with generic substitution. Table 4 presents the results of those calculations, for various levels of optimisation, i.e., various percentages of metformin preparations dispensed in the form of generics and the originator. For example, the optimal substitution of just 5% of packs of metformin originally dispensed as the originator would save the patients PLN 304,881, while saving the payer PLN 345,922. In case of drugs dispensed as generics, optimal substitution would generate a savings of PLN 541,851 and PLN 452,686 for the patients and NHF, respectively. Reaching the level of 100% optimisation would save the patients PLN 10,837,030 on generics and PLN 6,097,610 on originator drugs, making the total savings PLN 16,934,640. Relevant numbers for NHF would be similar, i.e., PLN 9,053,721 saved on generics, and PLN 6,918,443 saved on the originator, with a total of PLN 15,972,164 saved on the whole metformin market.

Table 4. Lost savings due to suboptimal implementation of generic substitution of metformin preparations prescribed and dispensed in Poland in 2019 (data refer to the dispensation period between 1 January–31 December 2019); NHF—National Health Fund; PLN—Polish zlotys.

		Metformin Preparations Dispensed in the Form of Generics (*N* = 13,717,759 Packs)		**Metformin Preparations Dispensed in the Form of the Originator (*N* = 5,863,087 Packs)**		**Whole Metformin Market (*N* = 19,580,846 Packs)**	
		Savings Lost by the Patient (PLN)	**Savings Lost by NHF (PLN)**	**Savings Lost by the Patient (PLN)**	**Savings Lost by NHF (PLN)**	**Savings Lost by the Patient (PLN)**	**Savings Lost by NHF (PLN)**
Optimisation premium (PLN/1 pack)		0.79	0.66	1.04	1.18	x	x
Optimisation level (%)	5	541,851	452,686	304,881	345,922	846,732	798,608
	10	1,083,703	905,372	609,761	691,844	1,693,464	1,597,216
	20	2,167,406	1,810,744	1,219,522	1,383,689	3,386,928	3,194,433
	30	3,251,109	2,716,116	1,829,283	2,075,533	5,080,392	4,791,649
	50	5,418,515	4,526,860	3,048,805	3,459,221	8,467,320	7,986,082
	75	8,127,772	6,790,291	4,573,208	5,188,832	12,700,980	11,979,123
	90	9,753,327	8,148,349	5,487,849	6,226,598	15,241,176	14,374,947
	100	10,837,030	9,053,721	6,097,610	6,918,443	16,934,640	15,972,164

The value of the total potential savings achievable, by means of optimised generic substitution, was compared to the whole metformin market in Poland in 2019. Figure 2 shows the percentage of savings that could be made, for both the patients and the payer, with the optimal use of generic substitution reaching 15.91% of total patient co-payments and 8.31% of total reimbursements incurred by NHF on prescriptions issued for metformin, respectively.



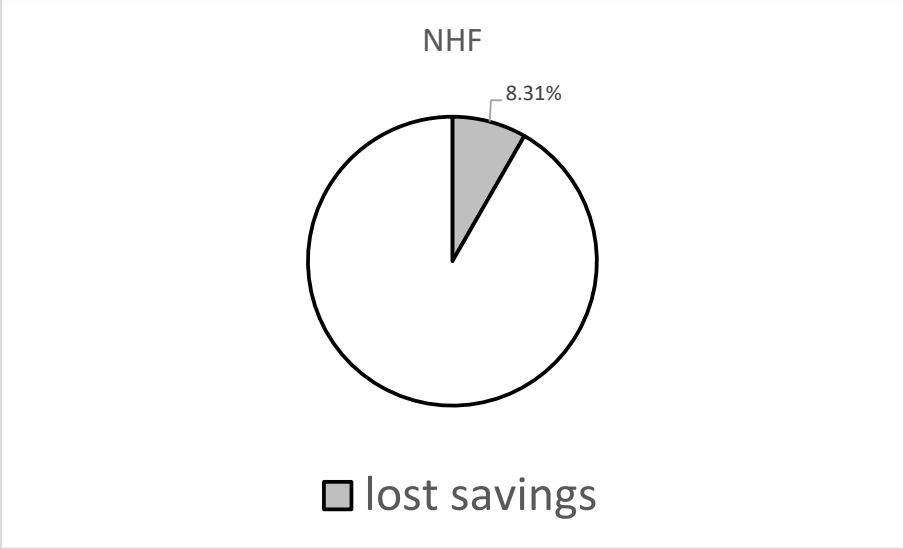


Figure 2. Potential savings that could be achieved by both the patients and the payer due to optimal use of generic substitution, expressed as the percentage of total co-payment (patients) and the percentage of total reimbursement (NHF), corresponding to all metformin prescriptions dispensed in 2019 in Poland. NHF—National Health Fund.

If the same proportion of achievable savings was compared to the total patient co-payment budget in 2019, which amounted to 3.253 billion PLN, potential savings for the patients could exceed 518 million PLN. In 2019, the NHF spent 9.455 billion PLN on the reimbursement of prescription drugs; therefore, potential savings, due to optimised substitution, could be estimated at 786 million PLN.

4. Discussion

To the authors' knowledge, this is the first large, nationwide, population-based study on the effectiveness of the implementation of the mechanism of generic substitution in Poland and one of very few, such wide-scale studies worldwide. Using real-world big data, we found a low prevalence of generic substitution applied to only 4.81% of packs dispensed, based on metformin e-prescriptions issued for its originator version. Another interesting observation was the even less frequent use of the same mechanism with e-prescriptions issued for various preparations of generic metformin, which were the subject of the further generic substitution in only 2.73% of dispensed packs, despite the potential savings the patients could obtain.

This suboptimal use of generic substitution was a reason the patients were losing large savings. Extrapolating our results to the total national metformin market in 2019, those lost savings were equivalent to nearly 16% of the total amount that the patients spent on the co-payments for various metformin preparations. In other words, the patients lost the chance of reducing their out-of-pocket co-payments by one eighth and to help their long-term adherence at the same time.

However, perhaps our most interesting finding was the fact that the patients' lost savings were parallel to the lost savings of the national payer, i.e., the NHF. Due to suboptimal use of generic substitution, the NHF lost a chance to save over 8% of the money spent on reimbursement of metformin preparations.

Thus, our findings prove that the optimised generic substitution of metformin could lead to a win-win scenario, i.e., along with increased affordability of drugs and its positive impact on patient adherence, it could lead to substantial savings for the national payer. If these findings are extended to the total Polish drug market, the potential savings achieved by both patients and the payer may be hundreds of millions PLN.

A study performed in 17 low-and middle-income countries showed that, on average, 60% (range: 9–89%) could be saved by an individual country from a switch in the private sector purchases from originator brands to the lowest-priced generics [25]. This strong financial incentive is turning many such countries, e.g., China, to the active promotion of the use of generics [26]. Nonetheless, high-income countries are also able to benefit from the use of generic substitution. For example, changes introduced in Greece (since 2010) aiming at the reduction of public pharmaceutical expenditure which, among others, included generic substitution, proved effective. The average price per package declined in 2013 by 28%, from EUR 17.8 in 2012 to EUR 12.8 in 2013 [27]. Similarly, in Ireland, claimants' costs were reduced by one-third when patients were changed to an equivalent cheaper, or generic, brand of proton pump inhibitor (PPI), while continuing on their original dose and quantity [28]. Therefore, European countries were advised to adopt various available measures to increase the use of generics, as a critical cost containment measure [29]. This approach was also reflected in the guidelines developed by the American College of Physicians, according to which clinicians are recommended to prescribe generic medications, if possible, rather than more expensive brand-name medications [30].

This, however, does not close the list of benefits provided by generic medicines, which offer much more to society than just their cost-saving potential through reduced prices. Apart from their cost-saving potential, generic medicines have an additional societal value by providing an easier access to pharmacotherapy, a stimulus for the innovation of pharmaceutical companies, and, last but not least, helping medication adherence [31]. A clear effect of the relationship between medication affordability and adherence was demonstrated in Catalonia, where the introduction of a fixed co-payment was followed by a statistically significant increase in initial medication non-adherence, which was reversed after the suspension of the fixed co-payment [32]. Similarly, in the USA, federal and state generic drug policies lowering cost-sharing were associated with an increase in patient's medication use and adherence [33].

Aiming to increase the relative consumption of generics and generic substitution, some countries adopted various interventions, such as prescriptions by an international non-proprietary name (INN) of an active ingredient. This ensures that the choice of a specific brand is based, to a lesser extent, on marketing and behavioural factors, and more on economic calculations. INN prescribing is mandatory in several European countries (for example, in Estonia, France, Greece, Spain, Netherlands, Portugal, Slovakia, and Italy) and outside Europe (Australia) [8]. Other interventions include increasing confidence in generics and promoting their acceptance by professionals, patients, and the general community, as well as incentivizing pharmacists and physicians to prescribe generics more frequently [25]. Such solutions are applied, for example, in France and Hungary. Specifically, in France, pharmacies receive bonuses for high rates of generic dispensation [34].

In order to further increase the use of generics, it is advisable to employ policies intended to affect prescribing behaviours among physicians, such as guidelines, information (about prices and less expensive alternatives), and feedback [35]. This direction is particularly worth exploring in Poland, as a survey conducted among physicians proved that many of them doubted the equivalence of generic and brand name drugs, which prevented them from prescribing less expensive drugs [36]. In the light of our findings, which prove that 30% of metformin prescriptions issued in Poland in 2019 were prescribed for the originator, this problem seems to remain unsolved.

Therefore, along with stimulating generic prescribing, another approach seems to be advisable, i.e., a wider use of generic substitution at the level of community pharmacies. The currently binding Polish legislation obliges community pharmacists to inform patients on the availability of less expensive drug equivalents whenever such equivalents are available. It is noteworthy that in the case of common drugs such as metformin, such availability is a rule. Our results prove, however, that this legislation is not effective in securing the optimal implementation of the substitution; therefore, the question is how to improve this situation. Perhaps, one of the reasons is that pharmacists are not always

aware of this obligation. A survey showed that one in five pharmacists (20.7%) did not know that each pharmacy had to inform patients about their option to replace a drug they had been prescribed with its less expensive equivalent [37]. Additionally, this obligation extends only to providing the patient with information of the option to obtain a substitute; however, there is no formal enforcement mechanism. Patients are free to purchase the brand of their choice, regardless of the availability of less expensive options. In such a case, patients' beliefs and opinions play an important role. These, however, are not necessarily supportive for generics. Although current evidence does not prove inferiority of generics, as compared to brand-name drugs [38], the existence of misconceptions may even lead to side effects and worse outcomes, due to the so-called nocebo effect [39]. Moreover, Polish patients tend to overestimate the choice made by the prescriber who issues a prescription (who is not necessarily fully aware of availability of less expensive drug equivalents). This, however, may discourage patients from accepting generic substitution offered in a community pharmacy [40]. As a result, substitution utilization varies, depending on the level of awareness of the pharmacist and the patient, as well as an availability of certain products.

In fact, even the mandatory generic substitution does not offer a complete solution of the problem. For example, the introduction of mandatory generic substitution in South Africa showed diverse effects of the use of generics and originators among four studied groups of drugs. After the implementation of the law, generic SSRIs replaced originator products, and the effect on ACE-I and calcium channel blockers was less pronounced; in case of PPIs, the intended effect of the policy was not observed [41].

Perhaps, further studies are required to establish which methods of optimisation of generic substitution implementation could work best in Poland. Nevertheless, our findings clearly prove that this direction is worth following, both due to the potential patients' savings for the patient and the payer, as well as the added value of improved medication adherence. Therefore, Poland should respond positively to the call, which urged governments to act appropriately and implement a coherent set of policies to increase the use of generic medicines [31].

There are several limitations of this study, which need to be considered. Firstly, metformin is an important drug for public health, because of its basic role in diabetes care. It accounts for a substantial portion of drug expenditures incurred both by patients and the national payer. Nevertheless, calculations based on this drug alone may not exactly reflect the overall tendencies in generic substitution, or its economic consequences in Poland. Secondly, in order to trace the pathways of substitution, we needed to limit our analysis to e-prescriptions, which constituted only one-tenth of the total volume of national prescriptions in 2019. Finally, our calculations of potential savings are based on the assumption that the least expensive generic is fully available, which is not always the case. This all could be a source of the potential bias of our model.

On the other hand, our analysis is the first one of this kind in Poland. Based on a large portion of the nationwide dispensation database, we were provided a unique opportunity to assess the extent and the economic consequences of generic substitution in real-world big data. A particular strength of our study comes with the use of methodology which gave grounds for the detailed assessment of the economic consequences of each individual episode of dispensing, regardless of whether it was associated with generic substitution or not, despite frequent changes of the reimbursement lists effective in the observed period.

Thus, we are convinced that this study provides new, important information, which can stimulate optimisation of the generic substitution implementation in Poland. Currently available national drug policy accepted the horizon of 2022 [8]; therefore, in its new version, these issues are undoubtedly worth tackling. Our findings prove that an optimised use of generic substitution can generate substantial savings to both patients and the national payer. Owing to better drug affordability, it may lead to an improved adherence, as well. We also hope that the win-win scenario, which we have identified, is a strong

incentive that will stimulate further research on generic substitution in Poland and abroad, in a search for the best practices of optimisation of this process.

5. Conclusions

This study was the first large, nationwide, population-based study on the effectiveness of the implementation of generic substitution in Poland. Real-world big data confirmed the low prevalence of generic substitution, applied to only 4.81% of packs dispensed, based on e-metformin prescriptions issued for its originator version (and with only 2.73% of those prescribed as various generic drugs). This suboptimal use of generic substitution was a reason for large savings lost by both the patients and the national payer. Thus, our findings indicate the need to optimize the implementation of generic substitution in Poland. It could not only lead to a win-win scenario, where both the patients and the national payer are secured substantial savings, but it could also have a positive impact on patient adherence.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data that support the study findings are made available by the authors with the permission of NHF (data owner). Restrictions apply to the availability of the data which were used under the license for this study.

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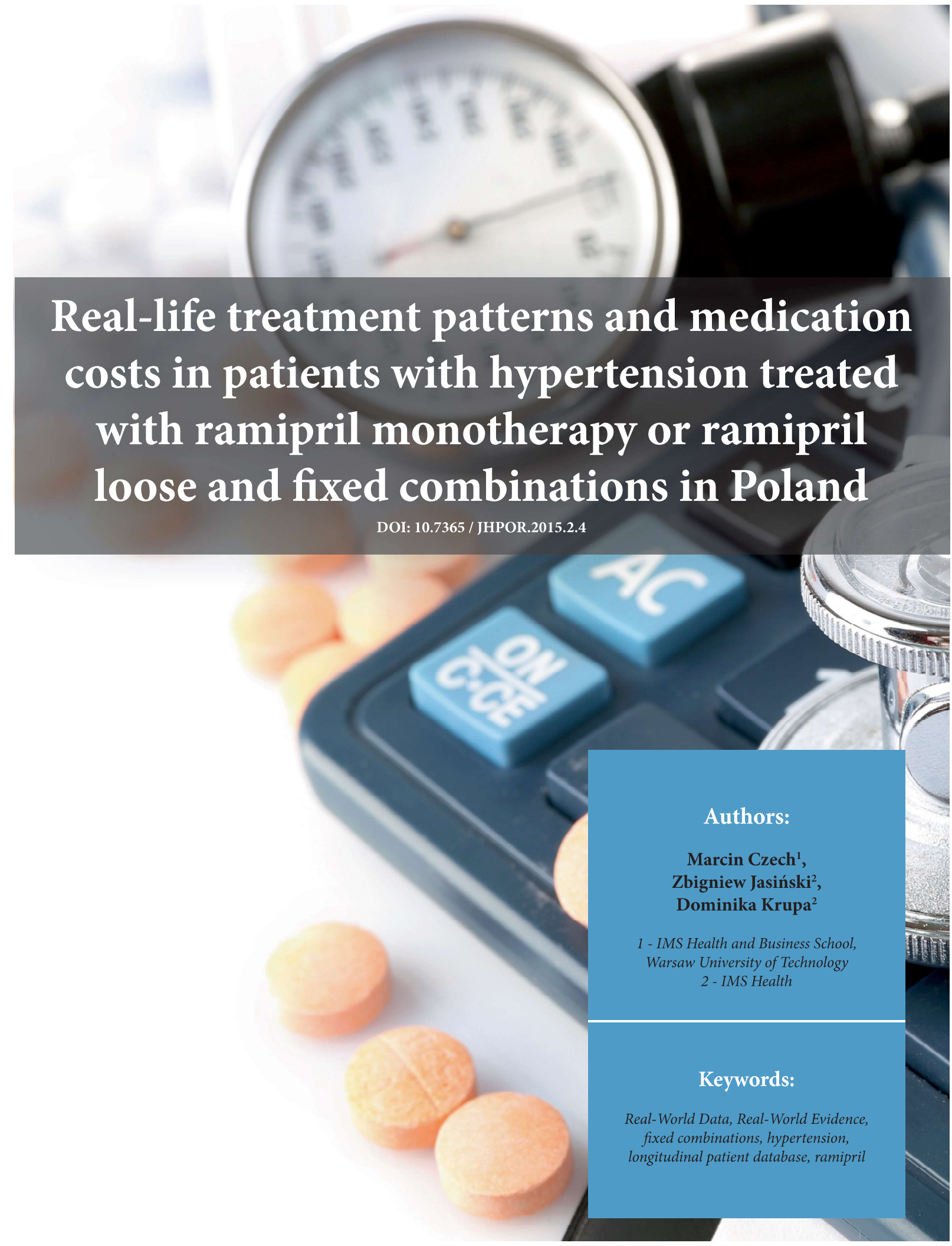
14.4 Appendix 4: Article 4

Czech, M., Jasinski, Z. & **Krupa, D.** (2015). Real-life treatment patterns and medication costs in patients with hypertension treated with ramipril monotherapy or ramipril loose and fixed combinations in Poland. Journal of Health Policy & Outcomes Research (Issue 2, s. 31–44). Fundacja Pro Medicina. https://doi.org/10.7365/jhpor.2015.2.4



Real-life treatment patterns and medication costs in patients with hypertension treated with ramipril monotherapy or ramipril loose and fixed combinations in Poland

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Keywords:

Real-World Data, Real-World Evidence, fixed combinations, hypertension, longitudinal patient database, ramipril

Abstract

Background: Real-World Evidence (RWE) provides insights into patient outcomes reflecting current practices under existing healthcare system conditions. Longitudinal patient data are a source of information that can be used to track treatments for anonymised individual patients over time. Arterial hypertension is one of the most common chronic diseases in Poland, leading to serious complications, especially if undiagnosed and not properly controlled. Fixed-dose combinations of antihypertensive drugs become more and more popular in the treatment of hypertension. The objective of this study was to analyze real-life treatment patterns and medication costs in patients with hypertension treated with the most popular ACEI in Poland - ramipril, in monotherapy, loose and fixed combinations.

Methods: This analysis was based on the longitudinal prescription database (IMS "LRx") of individual, anonymized patients structured by product, prescribing doctor specialty and patient age group and sex, sourced from dispensing transactions of 3367 chain and non-chain pharmacies, in the Polish open-care market. The period of analysis covers 20 months (January 2014 – August 2015). It is based on 1 488 053 patients and 9 023 582 prescriptions. Cost calculations were performed from payer's and patient's perspectives.

Results: Owing to the availability of multiple treatment options, patterns in hypertension treatment in Poland are very complex, even when considered only at the molecule level. Furthermore, switching to fixed-dose combination therapy based on ramipril resulted in savings for patients as well as the public payer.

Conclusion: Wider use of fixed-dose combinations is a cost saving option both for patients and the public payer.

Introduction

"The notion that evidence can be reliably placed in hierarchies is illusory (…). Observational studies too have defects but they also have merit. Decision makers need to assess and appraise all the available evidence". This statement made by Sir Michael Rawlins - the President of the National Institute for Health and Care Excellence - supports reaching beyond randomized controlled trials as a source of information on health technologies[1]. The term Real-World Evidence (RWE) or Real-World Data (RWD) comprises various types of data sets including information about epidemiology, effectiveness, safety, and costs of treatment, all generated and analyzed outside the framework of randomized controlled trials (RCTs)[2]. RWE provides insights into patient outcomes in a real-life setting, reflecting current practices under existing healthcare system conditions. It enriches information on efficacy obtained from clinical trials by adding data on effectiveness usually collected from a broader patient population (fig. 1).

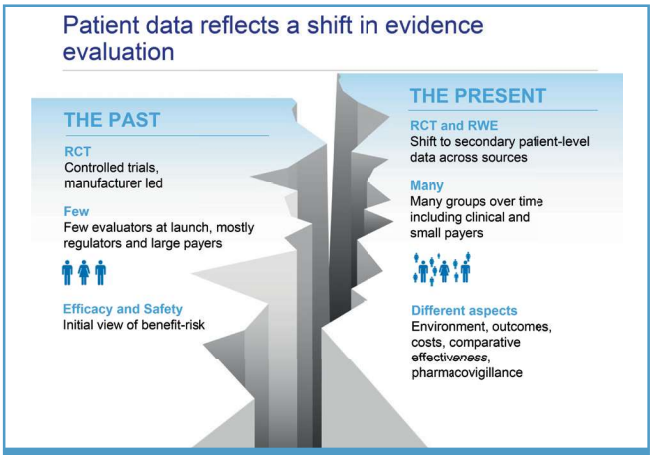

Figure 1. Main differences between randomized controlled trials and real-world evidence

RWE comprises a wide scope of data sources: electronic medical records (EMRs), (payers/insurers) claims data, national surveys, disease specific registries, surveillance systems, online communities, data on prescription patterns, marketing, sales and distribution, (human) genome data. If we treat these groups as primary data sources, then secondary sources based on processed, analyzed and researched data can be further distinguished. Observational studies frequently use retrospective data from administrative databases or EMRs. In contrast, a cohort study is a longitudinal study where a group of persons with the same characteristics and defined exposure is followed in time until the outcome of interest occurs. Sometimes patient-reported outcomes (PROs) are measured: in this case information is provided by patients themselves (fig.2)[2].

Among the main stakeholders using RWE in medicine and healthcare one can list: regulatory agencies, (state) payers, (state) insurance companies, healthcare providers, health technology agencies, clinicians, patients, manufacturers, and consultants. In Poland, key stakeholders have not yet fully embraced RWE as an evidence source, despite the fact that their involvement seems to be crucial in the further development of this domain. The recently performed analysis based on an exploratory survey to map current awareness and expectations of physicians, related to practical outcomes data, showed significant interest and broad spectrum of possible actions to improve

formal use of RWE in Poland[3]. Some of these efforts have already started: e.g. related to the health technology assessment (HTA) guidelines update currently performed by an expert group at the Polish Agency of Health Technology Assessment and Tariff System[4]. However, still few guidelines exist regulating usage of RWE in detail[2,5,6], and some of them are devoted to one type or one therapeutic area only[7,8].

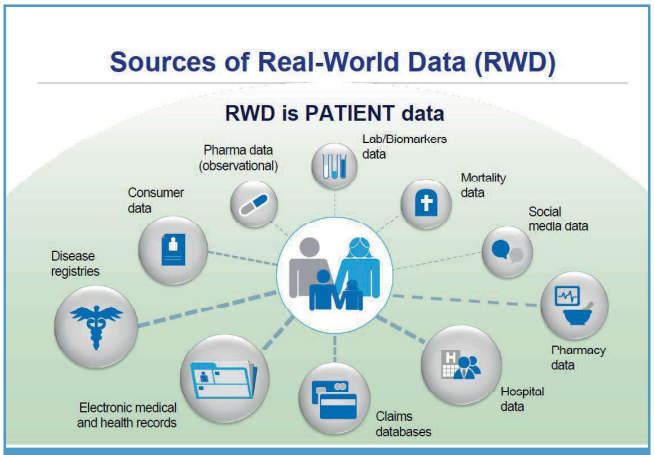

Figure 2. Sources of Real-World Data

Scientific quality and validity of information generated from RWE depend on sample size, representativeness vs. prevalence and incidence of the disease, completeness and clarity of the parameters coupled with the level of standardization[2].

Longitudinal patient data are generally considered as any anonymized patient- level information that can be tracked over time for an individual patient. In accordance with respective data privacy legislation, no personal data regarding patient, prescriber or pharmacy are collected or stored. As a result, such database contains exclusively anonymized information. Longitudinal patient information can help many stakeholders in the healthcare sector answer patient related questions, learn how medicine in real-world is practiced over time, along with actual treatment outcomes. This insight, coupled with cost data, can be useful in decision making processes leading to further optimized allocation of health care resources both at central, regional and individual practice levels[2].

Hypertension is one of the most common chronic diseases in Poland, leading to serious complications, especially if undiagnosed and not controlled properly. Ischemic heart disease, myocardial infarction and stroke are the leading causes of death worldwide and, despite a significant improvement[9], are still challenges for the healthcare sector in Poland. Diuretics, beta-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor antagonists and calcium antagonists are commonly used as a first-line therapy in arterial hypertension monotherapy. Unfortunately, monotherapy is often insufficient in controlling patients' condition, requiring treatment with more than one antihypertensive agent. Therefore fixed-dose combinations of antihypertensive drugs become more and more popular in the treatment of arterial hypertension. They are also recommended by many guidelines, including Polish ones, as an effective and relatively safe therapeutic option[10]. Still the efficacy of cardiovascular prevention is hampered by several problems including: monitoring; inadequate choice of medication; poor compliance and adherence to treatment; and sometimes cost of treatment. For these reasons all main stakeholders, medical professionals, (public) payers and patients themselves should be interested in selecting effective and cost-effective treatment options.

The objective of this study was to analyze real-life treatment patterns and medication costs in patients with hypertension treated with the most popular ACEI in Poland - ramipril in monotherapy, loose and fixed combinations.

Methods

This analysis is based on longitudinal prescription database of individual anonymized patients (IMS "LRx") structured by product, prescribing doctor specialty and patient age group and sex, sourced from dispensing transactions in the Polish open-care market, from 3367 chain and non-chain pharmacies (out of a total of 14 372 pharmacies in Poland in September 2015). All analytics are patient centric and market specific, calculated on an individual transaction basis collected every month from each pharmacy. Treatment dynamics considerations are based on a strict episode concept. Therapy episodes are calculated based on prescriptions and their durations. Free combinations of drugs in the same market caused by prescriptions on different days or by different doctors are taken into account in order to determine therapy combinations. If prescription duration is not available in the data, it is calculated based on existing information. Treatment pattern model was based on static and dynamic sub-models. The first one took into account initiation of treatment, treatment change and adding a new therapy to an existing one, as well as a permanent or temporary treatment termination. Continuation or restart of the therapy was considered in the static sub-model (fig. 3).

Figure 3 ▶

Patient Treatment Patterns: Key Performance Indicators (KPI)

Dynamic and Static Treatment Pattern, Treatment Duration Calculation

Group	KPI	Description with example (X=focus product, O=other product)	Last period		Present period
Gained	New	Therapy start with the focused Brand	-	-	X
	Win	Win from another therapy in the defined market		O	X
	Add-On	Therapy extension alongside an existing therapy		O	O+X
Static	Restart	Therapy restart of analyzed Brand after a gap of treatment	X	-	X
	Repeat	Remaining patients of the previous period with a relevant therapy episode in the current period		X	X
Awaiting	Off Drug	No active prescription in according month		X	-
Lost	End	No follow-up prescription for last 12 months after the last on drug period. The end classification substitutes the first temporary Off Drug classification.	-	-	-
	Loss	Loss to another therapy in the defined market		X	O
	Drop-Off	The focused product is stopped from a free combination		O+X	O

X represents a therapy episode of the focus therapy and O represents a therapy episode of a competitive therapy. Therapy episodes are calculated market specific based on prescriptions and prescription durations per patient.

Figure 3. Treatment pattern model

Patients on Drug

Monotherapy

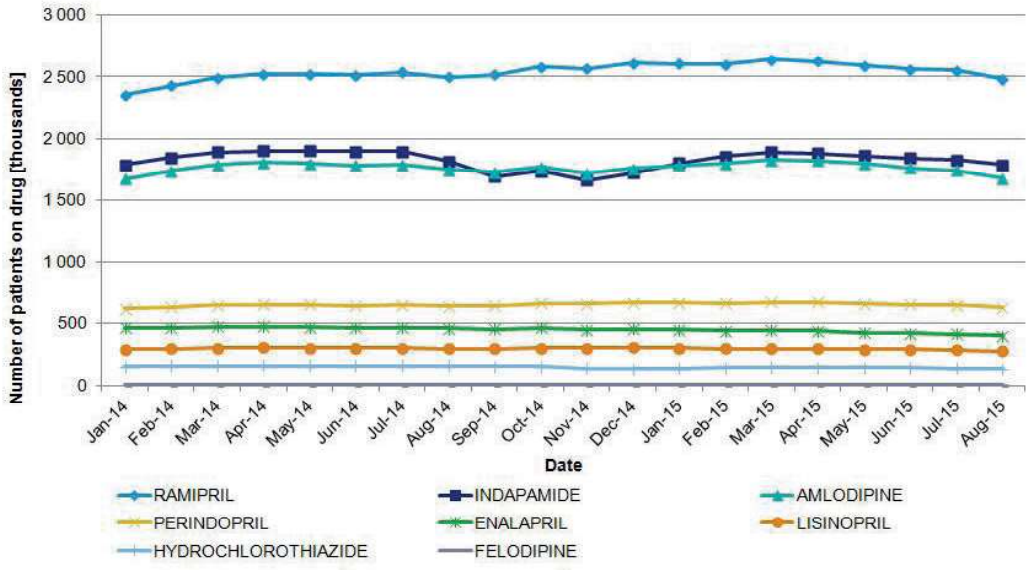

Figure 4. Number of patients treated with ACEI and related antihypertensive medicines

Total volume and value of ramipril and ramipril combinations market was derived from the IMS Pharmascope database, and prices sourced from the drug prices database IMS Refundator, created from the extant reimbursement list issued by the Ministry of Health as of November 2015.

Cost calculations were performed from payer's and patient's perspectives.

This analysis covers the 20 months period from January 2014 – August 2015. It's based on 1 488 053 patients and 9 023 582 prescriptions.

Results

Ramipril is the most frequently prescribed angiotensin converting enzyme inhibitor (ACEI) in Poland with approximately 300 000 patients treated. Its popularity was the primary reason this drug was chosen for analyses. The second most popular drug - perindopril - is used by approximately 80 000 patients. From January 2014 to March 2015 the number of patients treated with ramipril grew month on month to reach a plateau, since when there has been a slow decline. In the 21 month period under analysis, the number of patients on perindopril was relatively stable. Antihypertensive drugs from different therapeutic classes, as well as those used in fixed dose combinations like indapamide, hydrochlorothiazide or felodipine, were also analyzed for the same period (fig. 4).

A number of patients treated with a fixed dose combinations is much lower with 30 000 and 25 000 patients receiving perindopril- indapamide and perindopril- amlodypine products, respectively. Ramipril- amlodipine combination, although not the most commonly prescribed, is the most dynamically increasing group of products (fig. 5).

A detailed analysis of ramipril monotherapy treatment patterns shows the majority of patients repeat the treatment, there are a substantial number of off-drug patients in each period and there are many newly initiated patients (fig. 6).

Analysis of instances of combination therapy among hypertensive patients indicates the most dynamic growth in the use of ramipril-amlodipine preparations (fig. 7a) and more stable usage of ramipril-felodipine and ramipril-hydrochlorothiazide (fig. 7b and 7c).

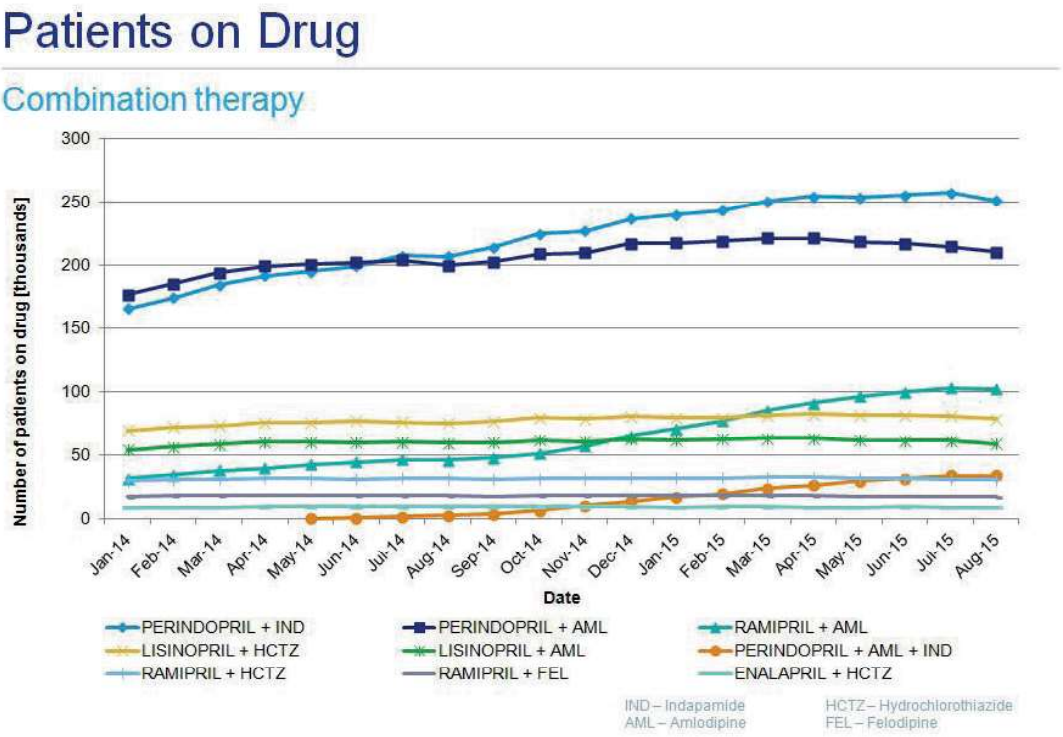

Figure 5. Number of patients treated with fixed dose antihypertensive combinations

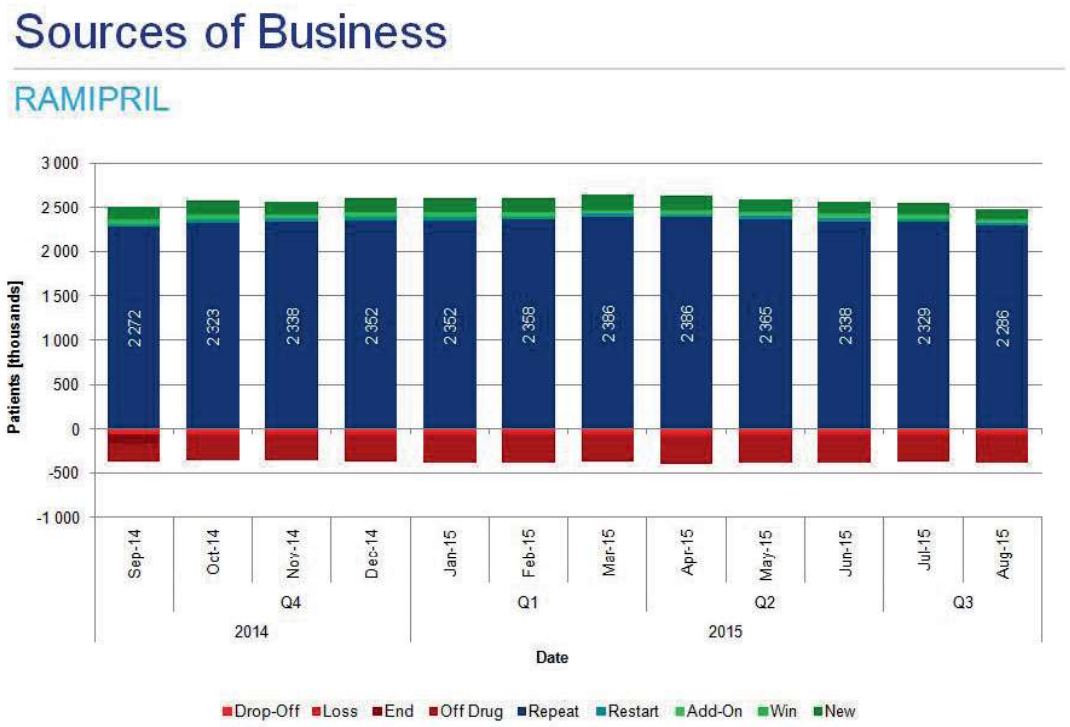

Figure 6. Treatment patterns in patients on ramipril

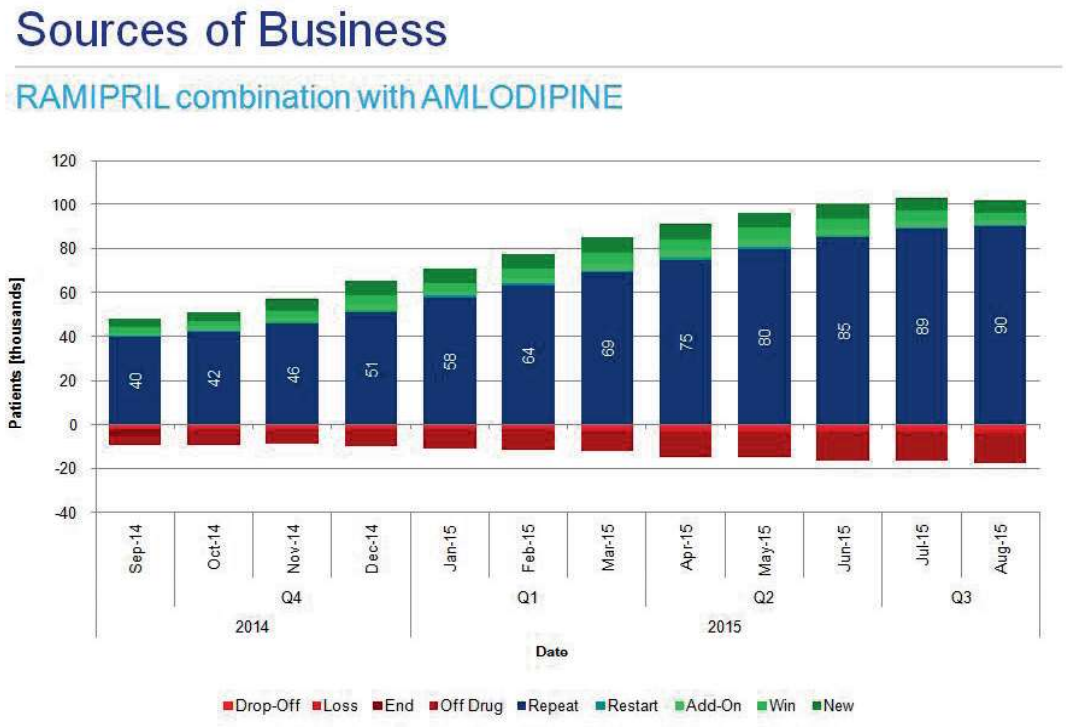

Figure 7a. Treatment patterns in patients on ramipril-amlodipine

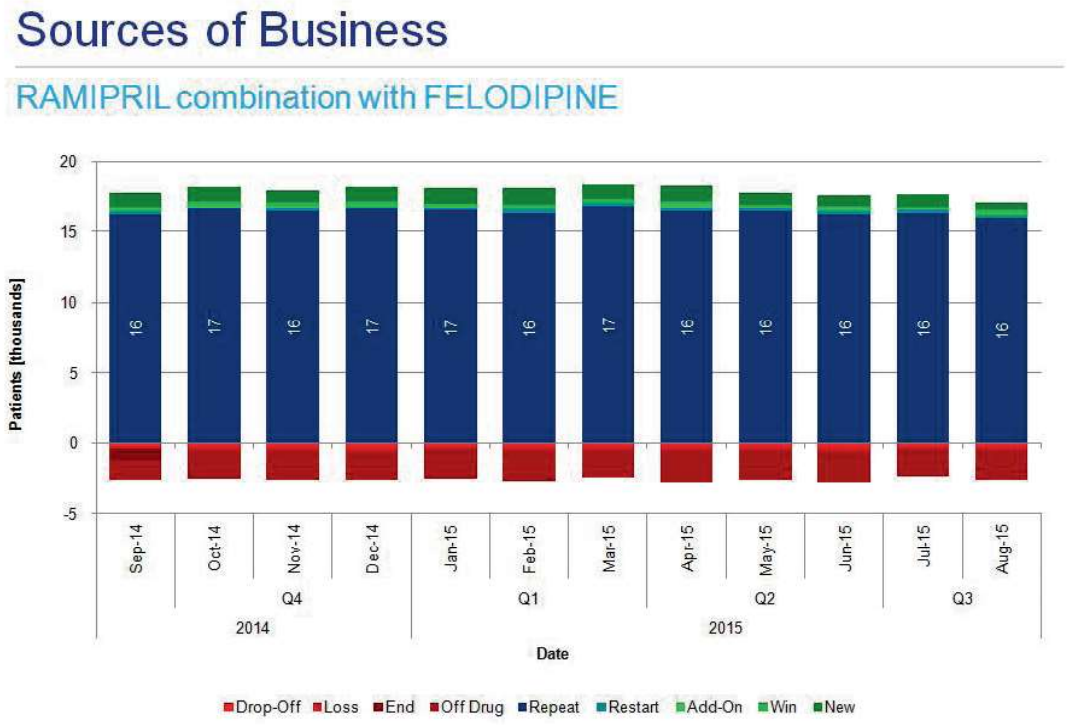

Figure 7b. Treatment patterns in patients on ramipril-felodipine combination

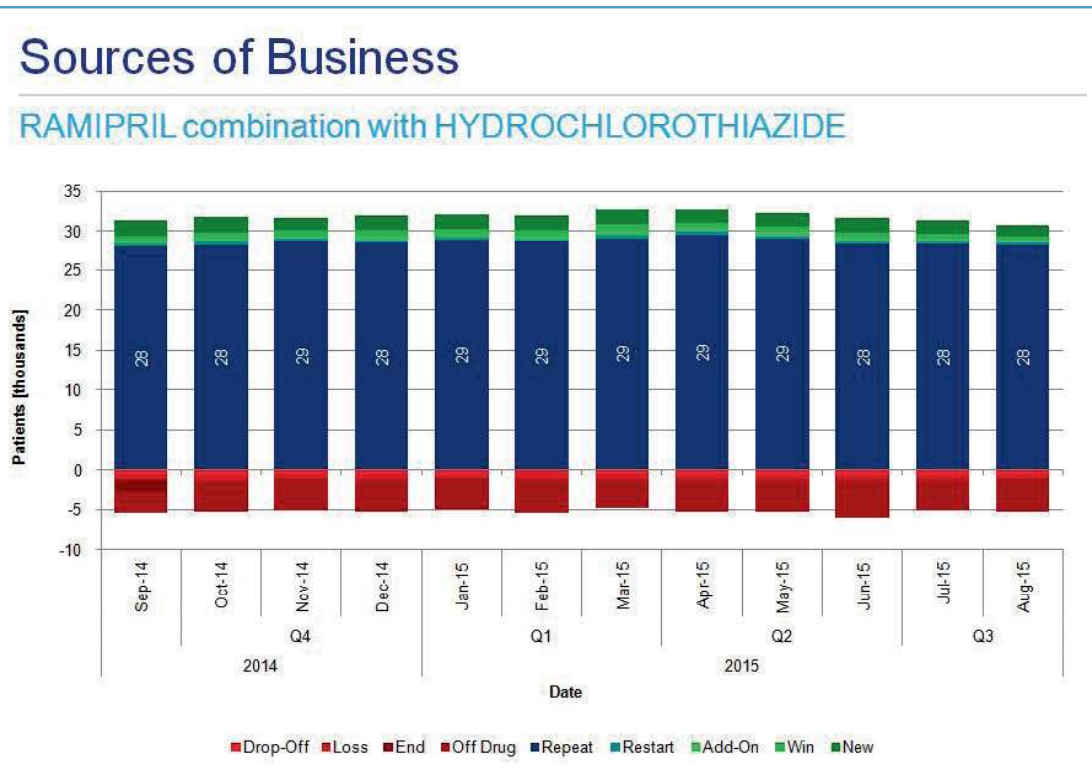

Figure 7c. Treatment patterns in patients on ramipril-hydrochlorothiazide combination

Both the initiation of hypertensive therapy and any subsequent changes are mainly prescribed by family medicine doctors and internal medicine specialists, with a less pronounced contribution from cardiologists (fig. 8 and fig. 9). This applies to ramipril monotherapy as well as fixed combination treatment.

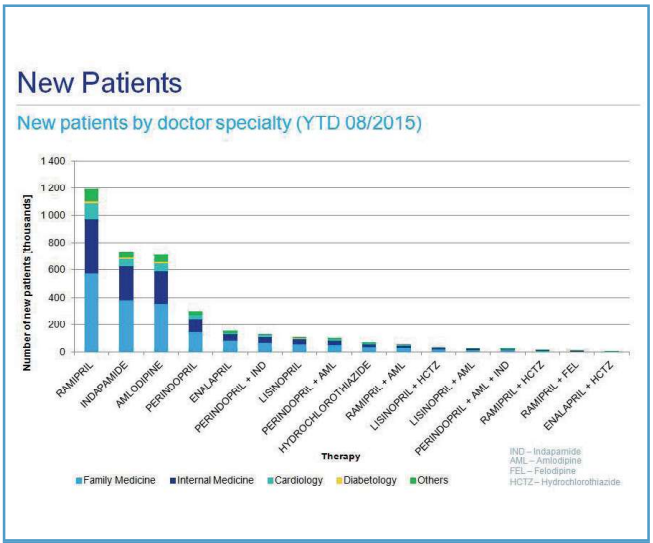

Figure 8. Initiation of anti-hypertensive therapy

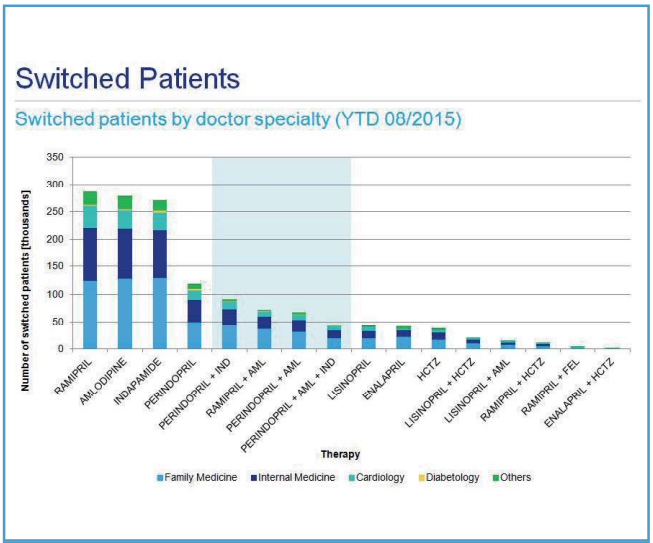

Figure 9. Changes in patients anti-hypertensive therapy

Owing to the multiple potential treatment options, treatment patterns in hypertension, even considered only at international names level, are very complex. They should be analyzed one by one with a certain degree of detail. For example: patients on a ramipril-amlodipine fixed combination would previously have been treated with ramipril alone, amlodipine alone, or a loose combination of these 2 drugs, or with another hypertension treatment (i.e. indapamide, perindopril, enalapril, perindopril-indapamide combination, lisinopril or others) (fig. 10). If one tries to consider all changes in ramipril-treated patients the picture becomes very complex (fig. 11).

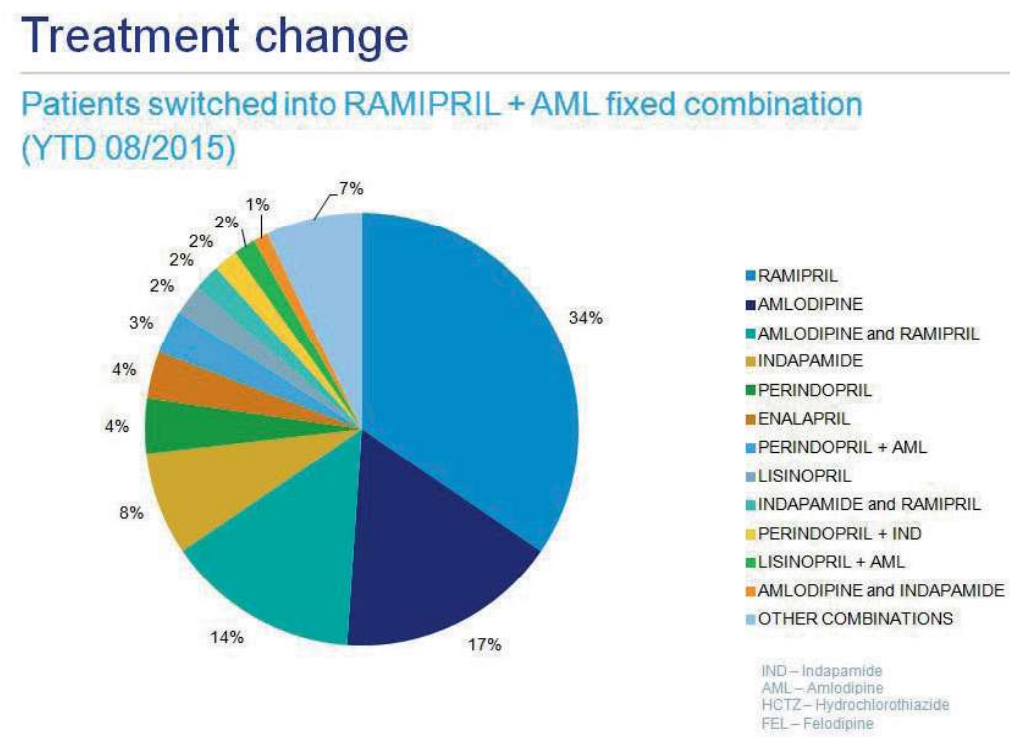

Figure 10. Previous treatment of ramipril-amlodipine treated patients

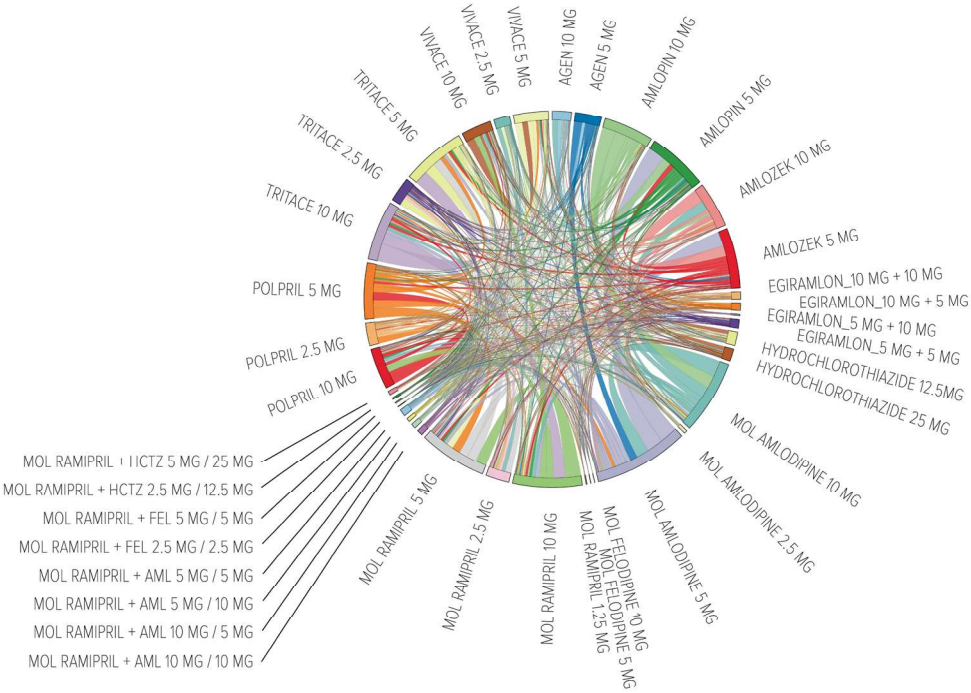

Figure 11. Ramipril switch matrix

	Molecule/combination	Annual Sales Volume*	Patient Cost [PLN]	Patient Cost % of total	NHF Cost [PLN]	NHF Cost % of total	Average Patient pack price [PLN]	Average NHF pack price [PLN]
1.	Amlodipine	14 970 449	99 159 132	51%	96 496 659	49%	6,62	6,45
2.	Felodipine	41 539	1 066 985	100%	0	0%	25,69	0,00
3.	Hydrochlorothiazide	1 298 784	11 006 350	100%	0	0%	8,47	0,00
4.	Ramipril	22 742 304	207 945 830	62%	128 126 262	38%	9,14	5,63
	Sum monotherapy	*39 053 076*	*319 178 297*	*59%*	*224 622 921*	*41%*	*8,17*	*5,75*
5.	Ramipril + Amlodipine	703 590	6 822 814	59%	4 704 180	41%	9,70	6,69
6.	Ramipril + Felodipine	165 170	2 340 181	78%	657 682	22%	14,17	3,98
7.	Ramipril + Hydrochlorothiazide	271 097	3 468 514	76%	1 081 386	24%	12,79	3,99
	Sum combination therapy	*1 139 857*	*12 631 509*	*66%*	*6 443 248*	*34%*	*11,08*	*5,65*
	SUM	**40 192 933**	**331 809 805**	**59%**	**231 066 170**	**41%**	**8,26**	**5,75**

**MAT 06/2015, IMS sell-in data*

Exchange rate (31.12.2015) 1 EUR = 4,2615 PLN; 1 USD = 3,9011 PLN

Table 1. Ramipril monotherapy, ramipril combination products and ramipril combination component drugs costs from patients' and NHF's perspectives

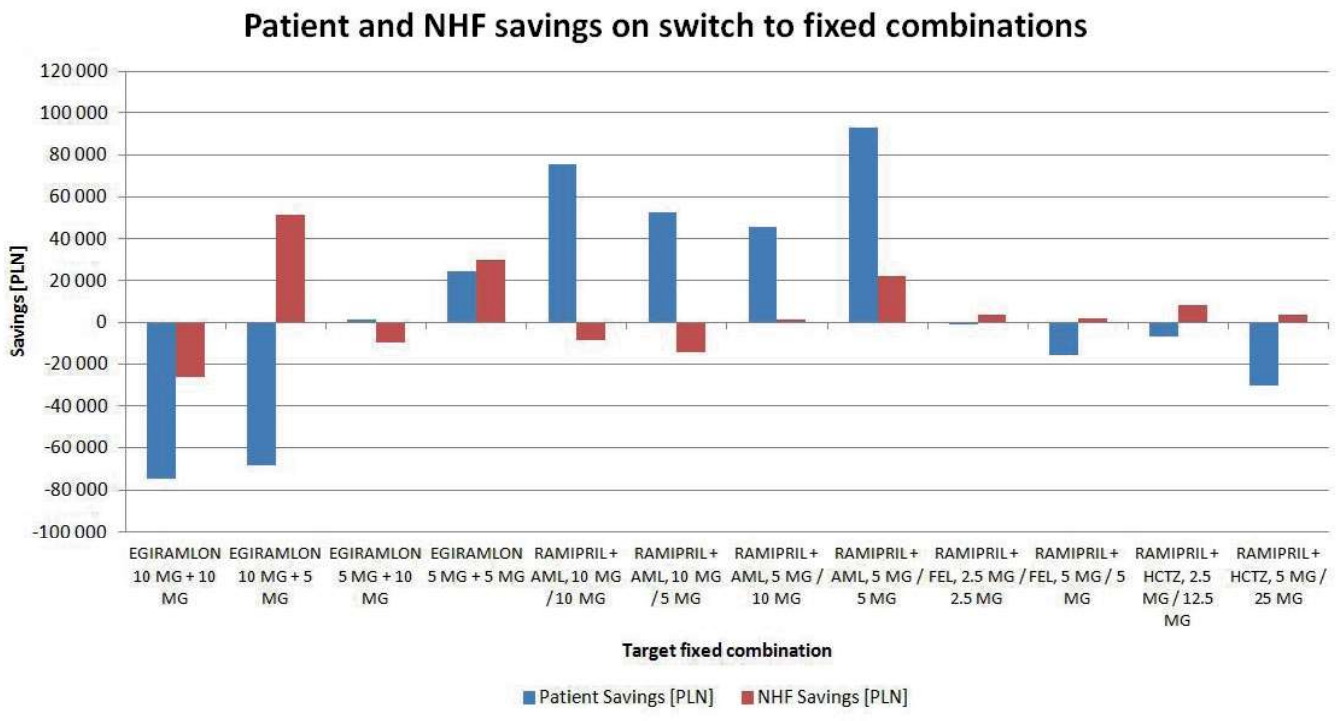

Figure 12. Savings for NHF and patients from switching to fixed dose combination ramipril-based therapy

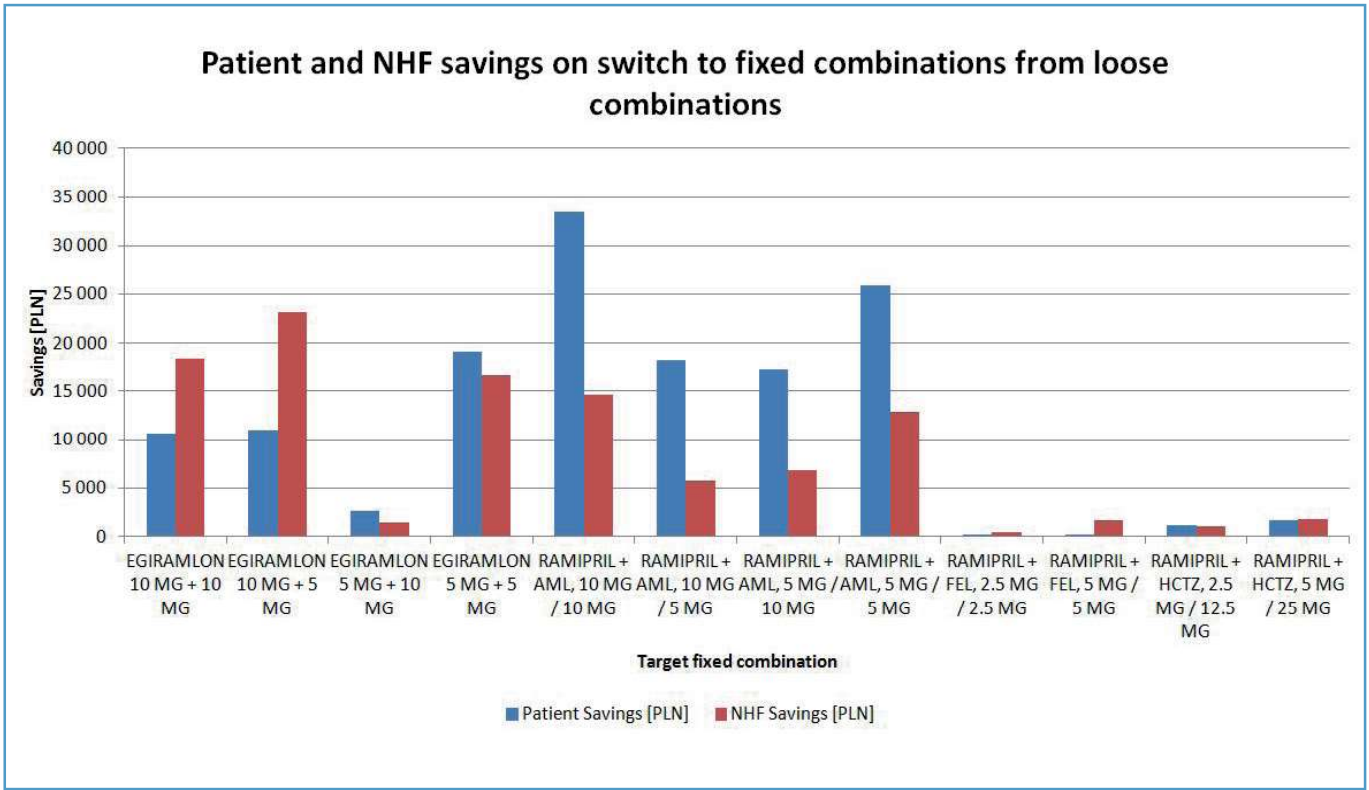

Figure 13. Savings from NHF and patients perspectives after switches from loose antihypertensive combinations to fixed dose combinations containing the same substances

Cost analysis over a one-year time period indicates more than 25 times higher the contribution of costs from monotherapy than the costs of fixed-dose combinations. For monotherapy treatments, patient co-payments are almost 45% higher than the cost covered by the National Health Fund (NHF). For fixed combination therapies, patient contributions are even higher in percentage terms (tab. 1). The total treatment cost for this sub-group of anti-hypertensive drugs is substantial, mainly due to the high prevalence of the disease (the drugs themselves are relatively inexpensive). In case of the two most popular molecules, ramipril and amlodipine combination therapy is more expensive on average for both the patient and NHF than in monotherapy, which might explain its limited popularity. However, when loose combination of these products is considered, savings are available on both sides. The same is true for molecules not reimbursed in monotherapy, felodipine and hydrochlorothiazide, but their popularity is limited compared to the two leaders.

Savings are available for both patients and the public payer arising from treatment switches to fixed dose combination therapy in ramipril and ramipril- related therapy (fig. 12). A cost increase is observed mainly when the dose of medication is also increased (in addition to unit costs).

If only switches from loose combinations to fixed-dose combinations are considered, only savings are observed (fig. 13). The scale of the savings however is small compared to the total spending on hypertensive drugs.

Discussion

Due to the scale of the phenomenon, effective and cos-effective therapy of hypertensive patients is needed by the society and payers.

Improved allocation of scarce healthcare resources in this therapy area, where so many reasonably priced medicines are available, would allow for funds to be reserved for the more complicated cases, while meeting the aims of primary prevention programmes. All these considerations should be made in a country- specific context reflecting specific healthcare conditions.

Similar studies on fixed-dose combination anti-hypertensive products, with reviews of the associated economics, were performed in neighbouring countries - Germany[11], and Ukraine[12] - leading to similar conclusions.

Longitudinal, patient centric databases serve as an ideal source of real-world information. In our study, we have analyzed treatment patterns in hypertension on a large, representative sample of the Polish population. We put special emphasis on fixed-dose combination products containing ramipril, and ramipril itself, as the most commonly used drug from the ACEI group. Medications from the same group have also been assessed previously in Poland, either from clinical perspective[13,14] or from economic[15], healthcare sector management[16] viewpoints.

There are limitations of our study, as follows:

1. Lack of effectiveness measures, even as secondary end points; it can be mitigated by including the results from large cohort studies performed in Poland
2. Compliance and persistence not measured; a longer time horizon would be more appropriate to meet this objective
3. Analysis includes only the cost of drugs, while other treatment cost components are missing. It can be argued however that these are irrelevant to this study and outside of its scope
4. Only selected hypertension treatment options included. Broadening the scope would require a modified approach but it is possible to be performed with the same methodology (for selected medications, group of drugs or for all anti-hypertensive products)

Further research and analysis are needed to respond to these limitations. On the other hand, however, to our knowledge this is the largest study to date of hypertension therapies using RWE datasets in Poland.

Conclusions

Anti-hypertensive therapy patterns are very complex among Polish patients. They can be analyzed in detail with RWE databases like IMS LRx. It is the only option to interpret patients behavior as well as doctors prescribing habits longitudinally in their real practice settings.

Analysis of the market leader in the ACEI group, ramipril and ramipril-based drugs indicate that a wider use of fixed-dose combinations versus loose combinations offers cost savings for both patients and the public payer. Savings also arise when patients are switched from ramipril monotherapy to fixed-dose combinations, especially when the dose is not increased.

Therefore a switch to fixed-dose combinations would be justified not only from clinical (where indication in individual patient exists) but also from the economic perspective. It is in line with current guidelines on anti-hypertensive treatment.

Ethical statement
No conflict of interest declared.
No funding received.
All authors are employed by IMS Health.

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14.5 Declarations of co-authors

Article 1

Marcin Czech

Ewa Chudzyńska

Beata Koń

Anna Kostera-Pruszczyk

Article 2

Marcin Czech

Jarosław Pinkas

Anna Mosiołek

Article 3

Przemysław Kardas

Aneta Lichwierowicz

Filip Urbański

Beata Szadkowska-Opasiak

Paweł Lewek

Ewa Karasiewicz

Marcin Czech

Article 4

Marcin Czech

Zbigniew Jasiński

…Warszawa, 16 maja 2024...
(miejscowość, data)

.....Marcin Czech.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Real World Evidence on the Effectiveness of Nusinersen within the National Program to Treat Spinal Muscular Atriphy in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Współtworzenie koncepcji pracy, nadzór nad projektem oraz korektę merytoryczną tekstu manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 15%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

współtworzenie koncepcji pracy, opracowanie metodyki, analizę danych, interpretację i wizualizację uzyskanych wyników oraz przygotowanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Marcin Czech
Elektronicznie podpisany przez Marcin Czech
Data: 2024.05.16 23:53:31 +02'00'

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

...Warszawa, 16 maja 2024...
(miejscowość, data)

.....Ewa Chudzyńska.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Real World Evidence on the Effectiveness of Nusinersen within the National Program to Treat Spinal Muscular Atriphy in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Przygotowanie danych surowych do dalszej obróbki oraz przeprowadzenie wybranych elementów analizy numerycznej

Mój udział procentowy w przygotowaniu publikacji określam jako 10 %.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

współtworzenie koncepcji pracy, opracowanie metodyki, analizę danych, interpretację i wizualizację uzyskanych wyników oraz przygotowanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Ewa Chudzyńska
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

…Warszawa, 23 maja 2024…
(miejscowość, data)

……..Beata Koń……..
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Real World Evidence on the Effectiveness of Nusinersen within the National Program to Treat Spinal Muscular Atriphy in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Walidację wyników oraz korektę finalnego manuskryptu pod kątem językowym i merytorycznym

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

współtworzenie koncepcji pracy, opracowanie metodyki, analizę danych, interpretację i wizualizację uzyskanych wyników oraz przygotowanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

……..Beata Koń……..
(podpis oświadczającego)

Signed by / Podpisano przez:
Beata Monika Koń
Date / Data: 2024-05-23 09:15

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

…Warszawa, 16 maja 2024...
(miejscowość, data)

.....Anna Kostera-Pruszczyk.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Real World Evidence on the Effectiveness of Nusinersen within the National Program to Treat Spinal Muscular Atrophy in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Walidację wyników pod kątem klinicznym oraz korektę finalnego manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

współtworzenie koncepcji pracy, opracowanie metodyki, analizę danych, interpretację i wizualizację uzyskanych wyników oraz przygotowanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Podpisano przez/ Signed by:
ANNA
KOSTERA-PRUSZCZYK
Data/ Date: 21.05.2024 10:00
mSzafir

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

…Warszawa, 16 maja 2024…
(miejscowość, data)

.....Marcin Czech.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Impact of COVID-19 Pandemic on the Use of Antidepressant and Antianxiety Pharmaceuticals as well as sick leave in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Współtworzenie koncepcji pracy, nadzór nad projektem oraz korektę merytoryczną tekstu manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 15%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 75 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

współtworzenie koncepcji pracy, opracowanie metodyki, analizę statystyczną danych, interpretację i wizualizację uzyskanych wyników oraz przygotowanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Marcin Czech
Elektronicznie podpisany przez Marcin Czech
Data: 2024.05.16 23:53:00 +02'00'

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

…Warszawa, 16 maja 2024...
(miejscowość, data)

.....Jarosław Pinkas.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Impact of COVID-19 Pandemic on the Use of Antidepressant and Antianxiety Pharmaceuticals as well as sick leave in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Pozyskanie danych do analizy oraz korektę finalnego tekstu manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 75 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

współtworzenie koncepcji pracy, opracowanie metodyki, analizę statystyczną danych, interpretację i wizualizację uzyskanych wyników oraz przygotowanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

...Warszawa, 16 maja 2024...
(miejscowość, data)

.....Anna Mosiołek.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Impact of COVID-19 Pandemic on the Use of Antidepressant and Antianxiety Pharmaceuticals as well as sick leave in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Weryfikację analiz pod kątem klinicznym oraz korektę finalnego manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 75 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

współtworzenie koncepcji pracy, opracowanie metodyki, analizę statystyczną danych, interpretację i wizualizację uzyskanych wyników oraz przygotowanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Podpisane elektronicznie przez Anna Izabela Mosiołek (Certyfikat kwalifikowany) w dniu 2024-05-16.

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

…Warszawa, 16 maja 2024...
(miejscowość, data)

.....Przemysław Kardas.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Potential to Reduce Patient Co-payment and the Public Payer Spending in Poland through and Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by Real-World Big Data Analysis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Opracowanie koncepcji pracy oraz współtworzenie metodyki badania, wybrane elementy analizy danych, współtworzenie manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 35%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

Współtworzenie metodyki analiz numerycznych oraz interpretacji wyników, przygotowanie opisu merytorycznego tła badania, współtworzenie manuskryptu, korekta finalnego tekstu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

.....
(podpis o ego)

Signed by / Podpisano przez:
Przemysław Kardas
Uniwersytet Medyczny w Łodzi
Date / Data:
2024-05-20 13:29

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

...Warszawa, 28 maja 2024...
(miejscowość, data)

.....Aneta Machnio (z d. Lichwierowicz).....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Potential to Reduce Patient Co-payment and the Public Payer Spending in Poland through and Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by Real-World Big Data Analysis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Współtworzenie metodyki badania, przygotowanie danych do badania, wybrane elementy analizy danych, współtworzenie manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 10%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

Współtworzenie metodyki analiz numerycznych oraz interpretacji wyników, przygotowanie opisu merytorycznego tła badania, współtworzenie manuskryptu, korekta finalnego tekstu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Aneta Machnio
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

…Warszawa, 16 maja 2024...
(miejscowość, data)

.....Filip Urbański.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Potential to Reduce Patient Co-payment and the Public Payer Spending in Poland through and Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by Real-World Big Data Analysis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Współtworzenie metodyki badania, nadzór nad projektem oraz korektę finalnego manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

Współtworzenie metodyki analiz numerycznych oraz interpretacji wyników, przygotowanie opisu merytorycznego tła badania, współtworzenie manuskryptu, korekta finalnego tekstu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Signed by / Podpisano przez:
Filip Urbański
Date / Data:
2024-05-28 16:14

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

...Warszawa, 16 maja 2024...
(miejscowość, data)

.....Beata Szadkowska-Opasiak.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Potential to Reduce Patient Co-payment and the Public Payer Spending in Poland through and Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by Real-World Big Data Analysis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Współtworzenie konceptu badania oraz korektę finalnego manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

Współtworzenie metodyki analiz numerycznych oraz interpretacji wyników, przygotowanie opisu merytorycznego tła badania, współtworzenie manuskryptu, korekta finalnego tekstu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Beata Szadkowska-Opasiak
.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

...Warszawa, 16 maja 2024...
(miejscowość, data)

.....Paweł Lewek.....
(imię i nazwisko)

OŚWIADCZENIE

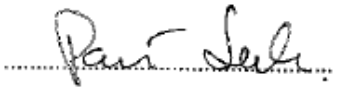
Jako współautor pracy pt. „The Potential to Reduce Patient Co-payment and the Public Payer Spending in Poland through and Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by Real-World Big Data Analysis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Współtworzenie konceptu badania oraz korektę finalnego manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

Współtworzenie metodyki analiz numerycznych oraz interpretacji wyników, przygotowanie opisu merytorycznego tła badania, współtworzenie manuskryptu, korekta finalnego tekstu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)


.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

...Warszawa, 16 maja 2024...
(miejscowość, data)

.....Ewa Karasiewicz.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Potential to Reduce Patient Co-payment and the Public Payer Spending in Poland through and Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by Real-World Big Data Analysis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Współtworzenie konceptu badania oraz korektę finalnego manusktyptu

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

Współtworzenie metodyki analiz numerycznych oraz interpretacji wyników, przygotowanie opisu merytorycznego tła badania, współtworzenie manuskryptu, korekta finalnego tekstu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

…Warszawa, 16 maja 2024…
(miejscowość, data)

.....Marcin Czech.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Potential to Reduce Patient Co-payment and the Public Payer Spending in Poland through and Optimised Implementation of the Generic Substitution: The Win-Win Scenario Suggested by Real-World Big Data Analysis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Współtworzenie konceptu badania oraz korektę merytoryczną manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 10%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

Współtworzenie metodyki analiz numerycznych oraz interpretacji wyników, przygotowanie opisu merytorycznego tła badania, współtworzenie manuskryptu, korekta finalnego tekstu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Marcin Czech
Elektronicznie podpisany przez Marcin Czech
Data: 2024.05.16 23:51:25 +02'00'

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

…Warszawa, 16 maja 2024…
(miejscowość, data)

.....Marcin Czech.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Real-life treatment patterns and medication costs in patients with hypertension treated with ramipril monotherapy or ramipril loose and fixed combinations in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Opracowanie koncepcji pracy, przygotowanie przeglądu literatury oraz części klicznej badania, a także współtworzenie pierwszej wersji manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 50%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 40 %,
(imię i nazwisko kandydata do stopnia)
obejmował on:

Analizę danych liczbowych wraz z opracowaniem metodyki tejże analizy, interpretację i wizualizację uzyskanych wyników oraz współtworzenie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy
(imię i nazwisko kandydata do stopnia)

Marcin Czech
Elektronicznie podpisany przez Marcin Czech
Data: 2024.05.16 23:52:23 +02'00'

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

...Warszawa, 16 maja 2024...
(miejscowość, data)

.....Zbigniew Jasiński.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Real-life treatment patterns and medication costs in patients with hypertension treated with ramipril monotherapy or ramipril loose and fixed combinations in Poland" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Przygotowanie części danych do analizy, ich ocenę pod kątem klinicznym oraz korektę finalnego manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 10%.
Wkład Dominiki Krupy w powstawanie publikacji określam jako 40 %,

(imię i nazwisko kandydata do stopnia)

obejmował on:

Analizę danych liczbowych wraz z opracowaniem metodyki tejże analizy, interpretację i wizualizację uzyskanych wyników oraz współtworzenie manuskryptu

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Dominiki Krupy

(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

Zbigniew Jasiński
LEKARZ
3634778

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników