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## IMPACT OF COMBINED FIXED-DOSE FORMULATIONS IN *HELICOBACTER PYLORI* ERADICATION ON INCIDENCE RATE OF GASTRIC CANCER IN UKRAINE FROM 2014 TO 2021

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**Key words:** *Helicobacter pylori*, eradication, gastric cancer, Ukraine  
**Ключові слова:** *Helicobacter pylori*, ерадикація, рак шлунка, Україна

**Abstract.** Impact of combined fixed-dose formulations in *Helicobacter pylori* eradication on incidence rate of gastric cancer in Ukraine from 2014 to 2021. Protas Y.O., Makarenko O.V., Duka R.V. A worldwide decrease in the incidence of gastric cancer and its most common form, adenocarcinoma, has long been observed. *Helicobacter pylori* (*H. pylori*) is a causative carcinogen for gastric adenocarcinoma. Triple and quadruple regimens for *H. pylori* eradication have been well identified and established. Aims of the research: this article aims to evaluate trends in the administration of combined drug therapy for *H. pylori* eradication and how this can impact gastric cancer rates in Ukraine. Defined daily doses (DDD) of the combined drugs for *H. pylori* eradication (years 2014-2020), gastric cancer, and gastric adenocarcinoma incidence rates in Ukraine from 2014 to 2021 were calculated and analyzed annually per 100,000 of inhabitants. The number of DDDs of the combined drugs used in *H. pylori* eradication increased by 27.28% ( $p < 0.0001$ ). The incidence of gastric cancer decreased by 26.56% ( $p < 0.0001$ ) from 2014 to 2021. Gastric adenocarcinoma was the most common form of gastric cancer comprising 94.56% (93.04–96.56%, 95% CI) of all cases. In Ukraine, the consumption of combined drugs for *H. pylori* eradication increased from 2014 to 2020, while the incidence of gastric cancer and gastric adenocarcinoma decreased from 2014 to 2021. Gastric adenocarcinoma is the most common form of gastric cancer in Ukraine. Use of these drugs might contribute to the decrease in gastric cancer incidence rate. These trends reflect global patterns.

**Реферат.** Вплив комбінованих препаратів у фіксованих дозах для ерадикації *Helicobacter pylori* на показники захворюваності на рак шлунка в Україні з 2014 до 2021 р. Протас Є.О., Макаренко О.В., Дука Р.В. В усьому світі вже давно спостерігається зниження захворюваності на рак шлунка та його найпоширенішу форму – аденокарциному. *Helicobacter pylori* (*H. pylori*) є канцерогеном, що викликає аденокарциному шлунка. Потрійні та четверні схеми ерадикації *H. pylori* є встановленими та чітко визначеними. Метою цієї статті є оцінювання тенденцій у застосуванні комбінованої медикаментозної терапії для ерадикації *H. pylori* та того, як це може вплинути на епідеміологічні показники раку шлунка в Україні. Розраховано та проаналізовано визначені добові дози (ВДД) комбінованих препаратів для ерадикації *H. pylori* (2014-2020 роки), захворюваність на рак шлунка та аденокарциному шлунка в Україні з 2014 до 2021 року щорічно на 100 тис. населення. Кількість ВДД комбінованих препаратів, що використовуються для ерадикації *H. pylori*, зросла на 27,28% ( $p < 0,0001$ ). Захворюваність на рак шлунка знизилася на 26,56% ( $p < 0,0001$ ) з 2014 до 2021 року. Аденокарцинома шлунка була найпоширенішою формою раку шлунка, що становила 94,56% (93,04–96,56%, 95% ІД) усіх випадків. В Україні вживання комбінованих препаратів для ерадикації *H. pylori* зросло з 2014 до 2020 року, а захворюваність на рак шлунка та аденокарциному шлунка знизилася з 2014 до 2021 року. Аденокарцинома шлунка є найпоширенішою формою раку шлунка в Україні. Використання цих препаратів може сприяти зниженню рівня захворюваності на рак шлунка. Ці тенденції збігаються з глобальними тенденціями.

Gastric cancer remains a leading disease in cancer-related mortality, despite extensive research on causative, contributing, and preventive measures. The most common form of gastric cancer is

adenocarcinoma. The causative roles of *Helicobacter pylori* (*H. pylori*) have been identified, and the incidence rate has slowly decreased worldwide [1, 2].

Currently, for the eradication of *H. pylori*, two main regimens are accepted worldwide: triple and quadruple therapy. Triple and quadruple regimens include a proton pump inhibitor (PPI). Triple therapy includes two antibacterial agents, in addition to a PPI. Quadruple therapy includes either three antibacterial agents or two antibacterial agents and a bismuth medication, in addition to a PPI [3].

In Ukraine, patients have the option of undergoing therapy either through a flexible combination of free doses of drugs or via a fixed-dose combined drug designed for *H. pylori* eradication. Within the pharmaceutical market of Ukraine, there are two available fixed-dose drugs, both of which embody triple therapy. The first consists of lansoprazole, clarithromycin, and tinidazole, while the second one comprises omeprazole, clarithromycin, and amoxicillin [4].

Due to the ongoing, incomplete, and complex digitalization of healthcare in Ukraine, there is no access to patient-linked data on *H. pylori*-bearing status and prescription of drugs, as well as the indications for them. Moreover, it is almost impossible to identify the prescriptions of individual brands of PPI, antibacterials, and bismuth medications exclusively for *H. pylori* eradication, although it is still possible to track the sales of combined fixed-dose drugs for *H. pylori* eradication because this is the only indication [5].

A parallel may also be drawn to historical pharmaceutical adverse effect incidents, such as the thalidomide tragedy, which underscored the importance of studying medication sales patterns associated with public health issues. Thalidomide, initially an over-the-counter (OTC) drug in Germany, was proven to cause congenital limb defects in children born to mothers who used it during pregnancy. The peaks in thalidomide sales were shown to correspond with the births of children with phocomelia, as revealed by Lenz in 1988 [6].

The present study aimed to investigate the dynamics of the consumption of combined fixed-dose drugs prescribed for the eradication of *H. pylori*, explore its potential effects on the incidence rate of gastric cancer and gastric adenocarcinoma, and evaluate the alignment of these trends in global patterns in Ukraine from 2014 to 2021.

#### MATERIALS AND METHODS OF RESEARCH

Data on the sales of combined drugs prescribed for the eradication of *H. pylori* distributed by pharmacies and hospitals in Ukraine from 2014 to 2020 were retrieved from PharmXplorer, a market research analytical system of the Proxima Research Company [7]. The number of DDDs per 100,000 person-years was calculated [8]. Information on gastric cancer and adenocarcinoma incidence was retrieved from the

National Cancer Register of Ukraine for the period from 2014 to 2021 [9]. The annual totals and annual incidence rates of gastric adenocarcinoma were calculated along with mean, standard deviation (SD), and 95% confidential intervals (95% CI) for adenocarcinoma. A polynomial regression model was applied to analyze trends in the number of DDDs and the incidence rates of gastric cancer and adenocarcinoma, and R2 values were calculated [10].

Compliance with ethical requirements. The studies were approved by the Bioethics Commission of the Dnipro State Medical University and in accordance with the principles of bioethics set out in the Declaration of Helsinki "Ethical Principles of Medical Research Involving Humans" and the "Universal Declaration on Bioethics and Human Rights (UNESCO)".

The data analysis was performed using MedCalc for Windows, version 20.2.18 (MedCalc Software, Ostend, Belgium).

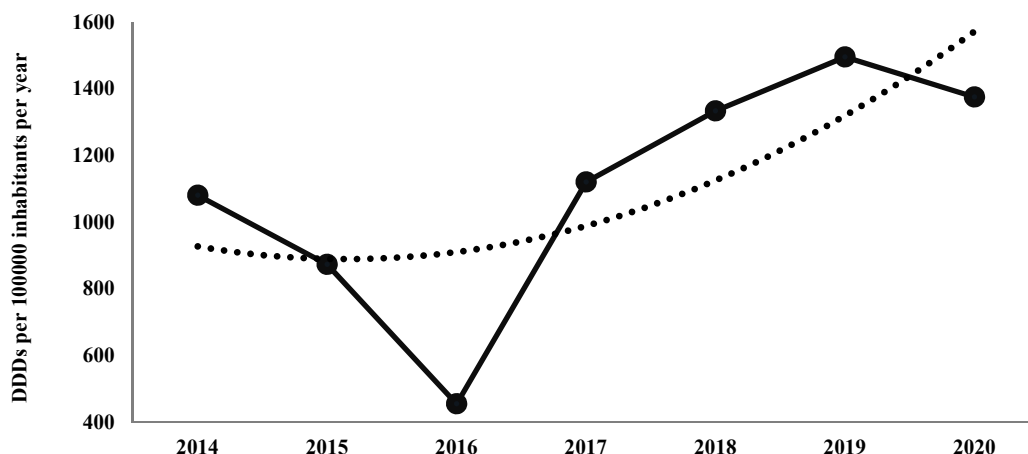
#### RESULTS AND DISCUSSION

The trend in DDDs for combined drugs for *H. pylori* eradication was unstable from 2014 to 2020. Three decreases were observed: (1) a 19.18% decrease ( $p < 0.0001$ ) in 2015 compared with 2014; (2) a 47.89% decrease ( $p < 0.0001$ ) in 2016 compared with 2015 – a significant increase in 2017, which was almost 2.5 times greater ( $p < 0.0001$ ) than in 2016; and (3) a decrease by 8.02% ( $p < 0.0001$ ) in 2020 compared with 2019 (Fig. 1).

The incidence rate of gastric cancer in Ukraine showed a gradual decline from 2014 to 2021. The lowest decline occurred in 2020, with a decrease of 28.13% compared with 2014 ( $p < 0.0001$ ) (Fig. 2A).

The results showed that adenocarcinoma was the dominant form of gastric cancer in Ukraine; it comprised 94.56% (93.04–96.56%, 95% CI) of all gastric cases from 2014 to 2021. The incidence rate of gastric adenocarcinoma also decreased by 30.74% from 2014 to 2020 ( $p < 0.0001$ ), which was the greatest decrease during this period (Fig. 2B).

The results showed an increasing trend in the number of DDDs of combined drugs for *H. pylori* eradication dispensed in both hospital and pharmacy settings from 2014 to 2020. This increase can be explained by several factors. First, the registration of new brands for the drugs in the Ukrainian pharmaceutical market is ongoing [4]. Second, medical practitioners may prefer to prescribe combined fixed dose drugs because of better compliance and higher adherence to pharmacotherapy, as was shown, for example, for arterial hypertension treatment [11]. The growing trend in administration of drugs for *H. pylori* eradication in Ukraine is also reflected worldwide [12].



The dotted black line is the polynomial regression line. Equation for the line:  $y=28.48x^2 - 124.2x + 1022.6$ ,  $R^2 = 0.5212$ .

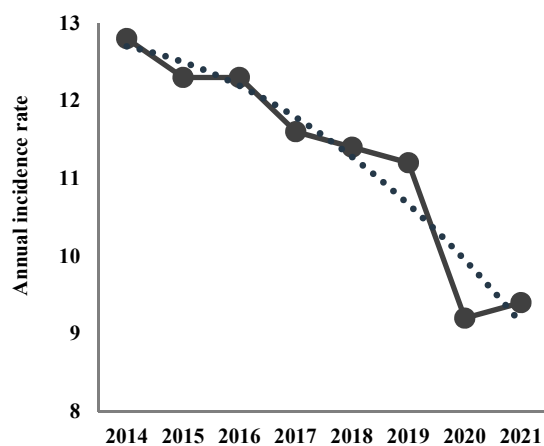
**Fig. 1. Dynamics of the use of combined drugs for *H. pylori* eradication in Ukraine from 2014–2020. DDDs per 100,000 inhabitants per year dispensed from hospitals and pharmacies in Ukraine (Y-axis)**

Regarding epidemiological indices of gastric cancer in Ukraine spanning the years 2014–2021, the results showed a decrease in the incidence rate of gastric cancer, including adenocarcinoma. Gastric adenocarcinoma was the most common type of gastric cancer in Ukraine during this period. These trends have also occurred worldwide [1, 2].

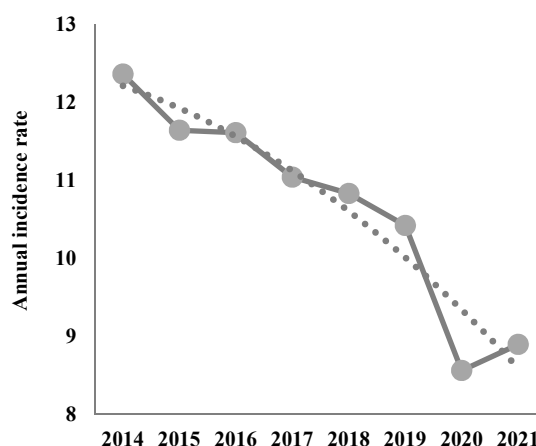
*H. pylori* eradication’s preventive effect on gastric cancer has been shown previously [13]. The increased use of fixed-dose combined drugs can play an important role in the decreased incidence rate of gastric cancer in Ukraine, as an effective elimination of the pathogen *H. pylori* plays a protective role against the development of gastric adenocarcinoma,

the main form of gastric cancer in Ukraine and worldwide [1, 2, 3].

Further studies are required to better understand the role of *H. pylori* eradication in gastric cancer prevention in Ukraine. A comprehensive dataset on Ukrainian patients – including individual-linked data on *H. pylori*-bearing status, acidity levels, usage of PPIs and other acid-lowering drugs, prescribed and available OTC, antibiotics, and other drugs (possibly protective against gastric cancer) on the outcomes of *H. pylori* eradication therapies and lifestyle – is required for a thorough investigation of the complex interplay of the factors in gastric cancer development [1, 2, 13, 14, 15].



A.



B.

The dotted dark grey line and the dotted light grey line are the polynomial regression line (equation for the dark grey:  $y = -0.0512x^2 - 0.0488x + 12.8$ ,  $R^2 = 0.9167$ ; equation for the light grey:  $y = -0.0384x^2 - 0.1713x + 12.42$ ,  $R^2 = 0.9176$ ).

**Fig. 2. Dynamics of the annual incidence of gastric cancer (A, Y-axis) and the annual incidence of gastric adenocarcinoma (B, Y-axis) in Ukraine per 100,000 people-year, 2014–2020**

## CONCLUSIONS

1. The consumption of combined fixed-dose drugs prescribed for the eradication of *H. pylori* increased in Ukraine from 2014-2020.
2. The incidence rate of gastric cancer and its main form, adenocarcinoma, increased in Ukraine from 2014-2021 (gastric adenocarcinoma was the most common form of gastric cancer during this period).
3. The trend in the increasing consumption of combined fixed-dose drugs for *H. pylori* eradication and the trend in decreasing incidence rates of gastric cancer are most likely related.
4. The trend of the increasing consumption of combined fixed-dose drugs for *H. pylori* eradication and the declining incidence rate of gastric cancer in Ukraine aligns with global data.

## Contributors:

- Protas Ye.O. – conceptualization, methodology, formal analysis, research, writing, visualization;  
 Makarenko O.V. – resources, management, project administration;  
 Duka R.V. – consulting, work administration.

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**Conflict of interests.** The authors declare no conflict of interest.

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