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History of smoking cessation treatment in Poland – the strengthening role of cytisine as the most effective and safe pharmacotherapy

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ABSTRACT

One of the greatest public health successes in Poland since the 1990s has been a decline in tobacco-related morbidity and mortality, including from lung cancer and cardiovascular disease. The steady decline in smoking cigarettes among adults in Poland during this period was among the most important factors contributing to this success. The key enabling factor in this process was the increasing range and availability of different pharmacotherapy supporting smoking cessation, including nicotine replacement therapy, but especially of the safe and affordable cytisine. The popularity of cytisine has been continuously growing among smokers in Poland. New developments in cytisine-based treatments and research in Poland and abroad can further strengthen global tobacco control efforts. Cytisine requires much greater interest from the medical community and from those responsible for public health in Poland.

KEY WORDS: smoking cessation, cytisine, varenicline, nicotine replacement therapy, Poland.

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INTRODUCTION

At the end of 1980s, Poland was a country with one of the highest levels of tobacco consumption as well as one of the highest rates of the prevalence of the smoking-related diseases in the world [1-6]. The public health actions that started at the beginning of the socio-economic transformation period in the early 1990s included a strategic national programme to reduce the health effects of tobacco consumption, as well as the adoption of the Parliamentary Act in 1995 [4, 7-11], led to a significant reduction in tobacco consumption and smoking frequency [4, 8]. Tobacco sales fell from about 100 billion cigarettes in the early 1990s to less than 40 billion in 2017 (Fig. 1) and prevalence of smoking declined from 73% in 1976 to 24% in 2019 in men, and from 30% in

1982 to 18% in 2019 in women [1, 12, 13] resulting in a significant reduction in the incidence and mortality from tobacco related diseases [1, 3, 14, 15]. Furthermore, according to the recent international publications, after 1990 Poland became one of the countries with the fastest decline in cigarette consumption as well as morbidity and mortality resulting from tobacco-related diseases (Figs. 1 and 2) [4, 6, 14-17]. A good illustration of this phenomenon is the decreasing trend in mortality from lung cancer in young and middle-aged male and female population (Fig. 2) and from cardiovascular diseases (Fig. 3). The lung cancer is a disease that almost solely occurs in smokers [3, 4], while adult cardiovascular diseases are said to be caused by cigarette smoking in about 30-50% cases in the European countries [18].

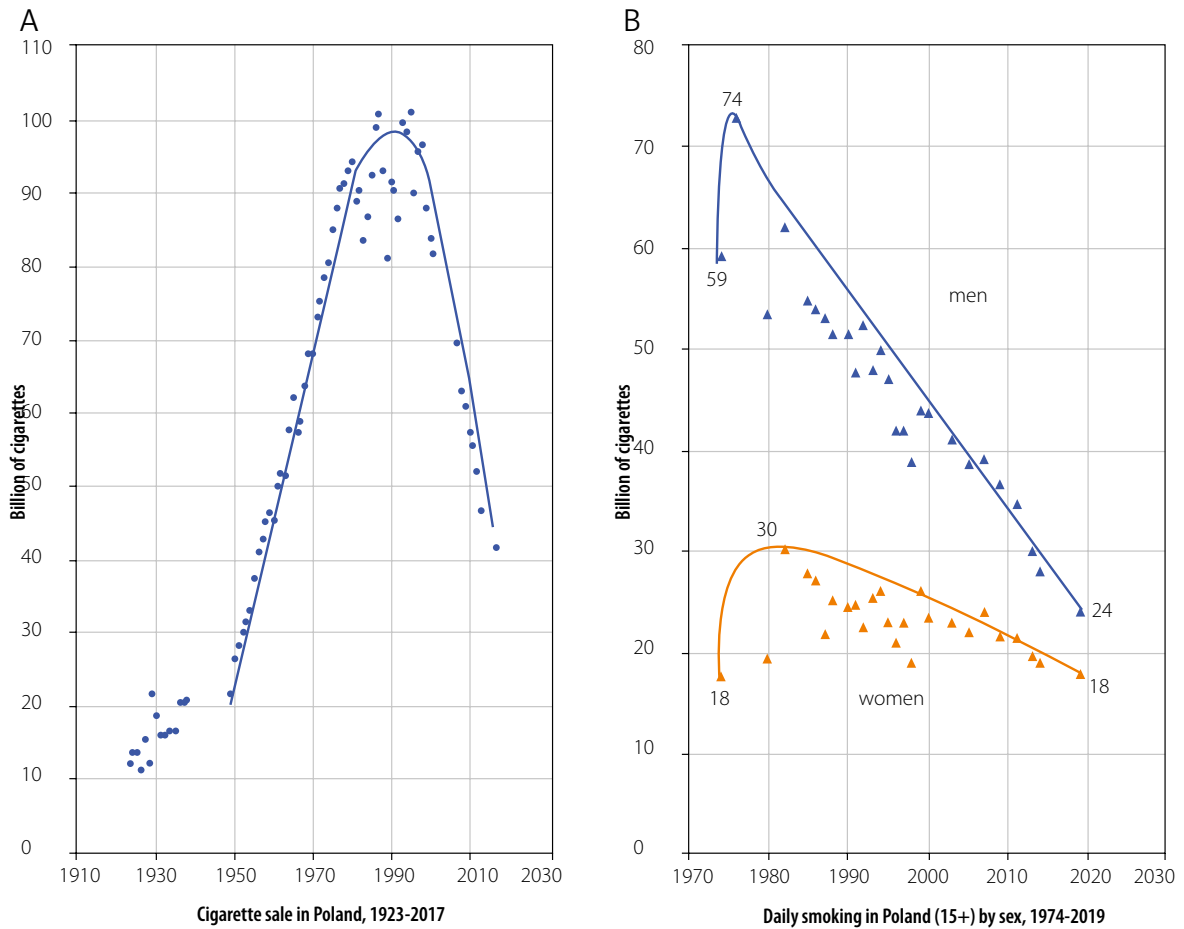


FIG. 1. Cigarette sale (A) and prevalence of daily smoking (B) in Poland [1, 12]

HISTORY OF SMOKING CESSATION TREATMENT IN POLAND

Smoking cessation pharmacotherapy seems to be an important factor contributing to the decrease in the consumption of cigarettes in Poland, especially in the last decade.

The market for modern, science and evidence-based medicines to treat tobacco dependence has only been developing worldwide since the early 1980s [19-22]. In the recent decades in Europe there have been few drugs of scientifically proven effects sold on the market. Currently, their sale adds up to hundreds of millions of packages sold annually [19-22] and the market continues to grow. A commonly used and often available without a prescription primary treatment for quitting smoking, recommended by the World Health Organization (WHO) is nicotine replacement therapy (NRT). It works by replacing nicotine from cigarettes for chemically pure nicotine. This chemically pure nicotine is delivered in many forms, including as a gum, patches, lozenges, tablets, inhalers, nasal and mouth spray, and stripes. The first NRT treatment was produced in the form of a “chewing” gum and was sold under the trade name “Nicorette®”. It

was introduced to the market in the early 1980s by the Swedish pharmacological company “Leo” [23].

This group of substances used for tobacco dependence treatment has been introduced onto the Polish market already in 1980s, just a few years after their debut in Sweden. The fast-track introduction was made possible thanks to the pressure of Polish oncologists and NRT was first sold in so called Pewex chain shops where items could be purchased only using hard currency, primary USD. Thanks to this, NRT has quickly gained prestige and popularity among smokers in Poland. Sales of all types of NRT have increased in Poland from about half a million of packages per year at the beginning of 2000 to over 3 million in 2019 [24].

In the 1990s, another class of smoking cessation drugs that interact with receptors in the brain were developed. Bupropion was introduced to the market first (sold under the name Zyban™), followed by varenicline (sold under the name Champix® in the European Union (EU) and Chantix® in the USA). Varenicline was synthetically manufactured in the 1990s by Pfizer, but its natural counterpart – cytosine – on which the varenicline’s chemical and biological properties were modelled,

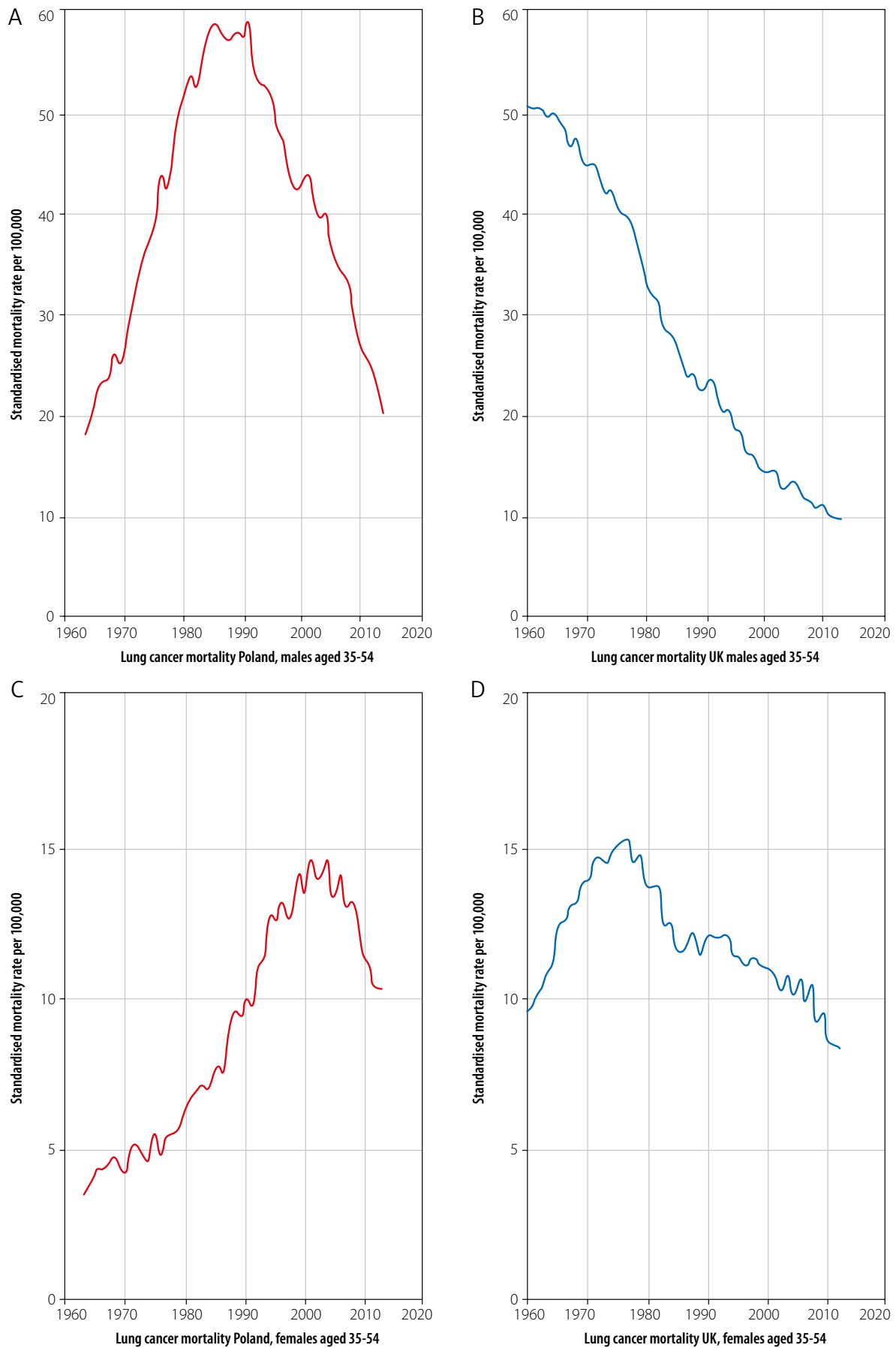


FIG. 2. Lung cancer mortality, age group 35-54, males and females, Poland vs UK [2, 3]

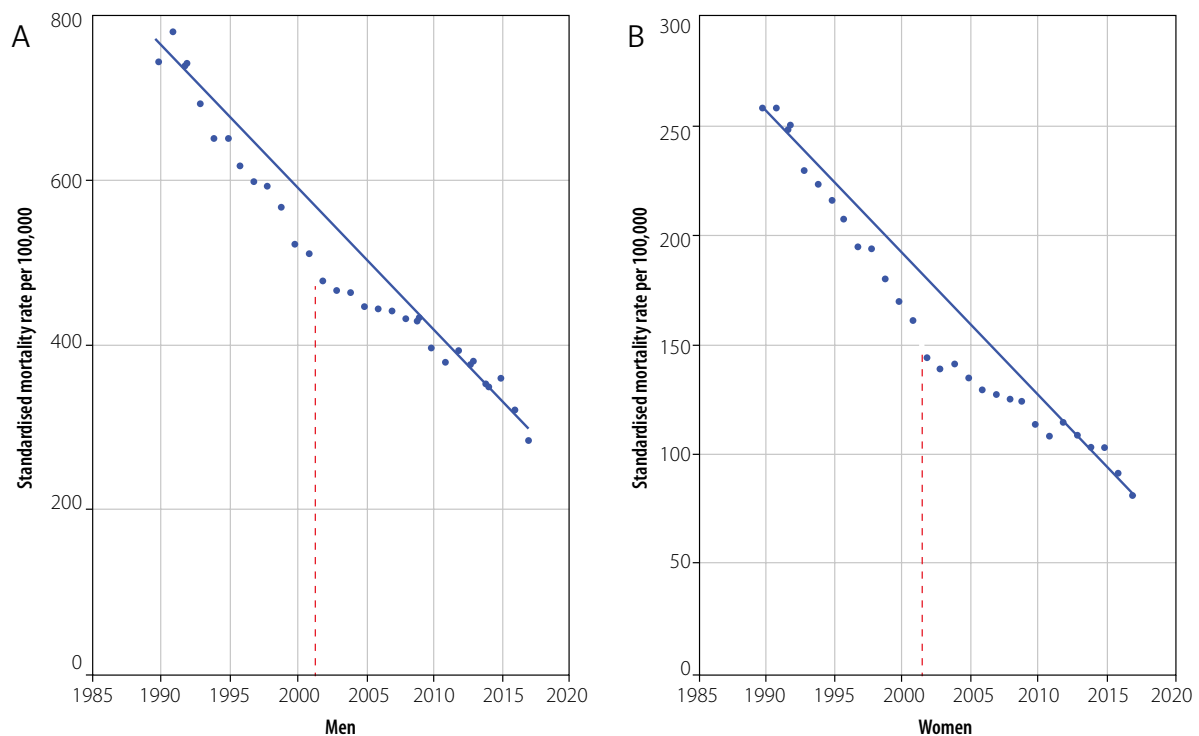


FIG. 3. Time trend of mortality due to cardiovascular diseases (CVD) in age group 45-64 years, Poland (source: WHO Mortality Database; mortality rates standardised per world standard population)

has been present in the countries of Eastern Europe since 1960s already [25-27]. Cytisine and varenicline belong to the same group of partial agonist and a partial antagonists of nicotine receptors [25, 27]. Both substances have a high affinity for the $\alpha_4\beta_2$ nicotinic receptors. As cytisine, varenicline block nicotine receptors in brain and keep them prevent from binding with nicotine. Pharmacological impacts of cytisine and varenicline administration are a reduction of satisfaction with smoking and a decline of nicotine craving, which occurs after a period of abstinence from tobacco [20, 28-36]. In most countries of the world, including the US and all western EU countries, varenicline became a very popular smoking cessation treatment, together with the NRT [19-22]. Varenicline is considered the most effective smoking cessation treatment in Western countries, especially in comparison to NRT and when combined with behavioural support [37, 38]. However, varenicline has been available only on prescription with the cost of the therapy very high in countries with no or limited reimbursement for smoking cessation therapy. Moreover, although safe [39], varenicline use is nonetheless associated with some side effects. For all these reasons, there has been a long-standing discussion among smoking cessation experts on the similarities and differences between cytisine and varenicline and the benefits of using cytisine [40, 41].

The Polish market for the treatment of smoking addiction is very different from that of the western countries. The main difference between Poland and the other

western countries is the availability and sale, on a population scale, of a plant-based drug called cytisine. While in 2019 there were 6.8 million of smokers in Poland [13], the annual sale of cytisine alone reaches hundreds of thousands of packages. This drug was developed over half a century ago by two visionary Bulgarian scientists, XD Paskov and VK Dobrev in Bulgaria [42-47] and it was in use for several decades in many eastern European countries that were under the Soviet Bloc rule, but on a very small scale [20, 29, 30, 40, 48-54].

Cytisine is a plant-based alkaloid. It is obtained from the extract from the *Laburnum anagyroides* tree, commonly called “false tobacco” or “golden rain” found in central and southern Europe, as well as from the *Kowhai* tree native to New Zealand. Cytisine has a chemical structure and receptor binding mechanism similar to that of nicotine. It is a partial agonist of $\alpha_4\beta_2$ -cholinergic nicotine receptors in the brain. Being the agonist, it acts like nicotine and stimulates dopaminergic neurons whilst on the other hand blocking nicotine receptors in brain and keep them prevent from binding with nicotine. This effect is weaker than in the case of nicotine delivered from cigarette smoke, the release of dopamine is slower and less intense. However, the release of dopamine relieves the syndrome of nicotine withdrawal [27, 35, 36, 55-57].

Cytisine has been present on the Polish pharmacological market since the 1970s, but initially it was rarely used [58, 59]. Its sale before 2000 was about 20-40 thousand packages per year (Figs. 4 and 5). However, after the

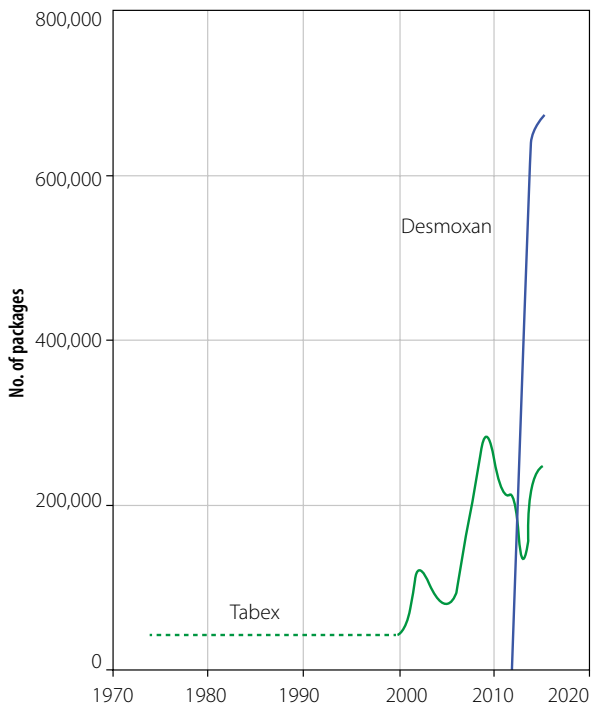


FIG. 4. Cytisine sale (Tabex and Desmoxan) in Poland until 2015 [19, 53]; prepared on the basis of data from IMS Health Poland

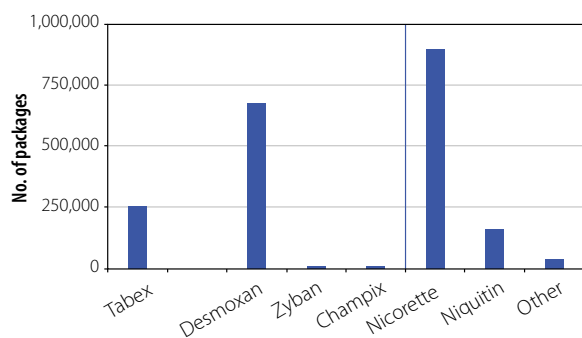


FIG. 5. Sale of smoking cessation drugs in Poland in 2015 [19]; prepared on the basis of data from IMS Health Poland

socio-economical changes and the preparation of Poland to join the EU in 2004, the pharmaceutical records of cytisine were questioned and considered to be insufficient for the registration of the drug in the EU. Under the pressure from the medical community in Poland, mostly cancer researchers, the Polish Ministry of Health had agreed to conditional registration of the drug under the condition of undertaking modern clinical trial assessing the efficacy and safety of cytisine [20]. For many years, Cancer Center in Warsaw became a centre of tobacco control activities in Poland and the Director of Epidemiology and Prevention Division was a co-chairman of the National Tobacco Control Commission by the Ministry of Health.

A research group from the Department of Epidemiology of the Cancer Centre in Warsaw under the leadership of the first author of this paper (WZ) has started an extensive research on cytisine. These studies were conducted in good cooperation with the producer of the drug (Sopharma, Sofia, Bulgaria), who made drugs available for research [28]. First, an open observational clinical trial into the safety and effectiveness of cytisine was conducted [60, 61]. Then, in collaboration with a renowned group of researchers from the University College London, a double-blind placebo-controlled clinical trial, the so-called Tabex Smoking Cessation trial (TASK) was conducted. The principal investigators on the trial were Professor Witold Zatoński from the Cancer Centre in Warsaw and Professor Robert West from the University College London in the UK [62].

In 2011, the New England Journal of Medicine (NEJM), one of the most influential medical journals, published the results of this first randomised clinical trial of cytisine. The trial was conducted in accordance with the contemporary EU regulations for clinical trials, and have showed that cytisine is almost 3.5 times more effective for smoking cessation than placebo, and is safe [20, 62]. The report prepared for the Polish Ministry of Health by the first author of the publication (WZ) and his research team allowed for the unconditional registration of cytisine as a pharmacological drug in Poland. At the same time, cytisine was recognised to be sufficiently safe to be sold through pharmacies without a prescription. Consequently, in accordance with the Polish Anti-tobacco law from 1995, cytisine advertisement as a stop smoking medication was allowed in the media, including on the TV [7, 53].

Publication of clinical trials in NEJM, promotion of cytisine at numerous scientific congresses, success in the field of tobacco control in Poland [11, 63, 64], have all contributed to the beginning of wide interest in this cytisine drug in many countries around the world. This was the beginning of interest of Polish drug manufacturers in smoking cessation. It had led to the production of new cytisine-based treatments on the Polish market under the trade names Desmoxan and Recigar [53], next to the Tabex produced by Bulgaria.

OTHER TOBACCO CONTROL ACTIVITIES IN POLAND

At the same time, since the beginning of the 1990s, extensive public health and tobacco control activities have been initiated in Poland to create a national system to aid treatment of tobacco [20, 21, 60, 64]. Janik-Koncewicz *et al.* [19] described the constituent factors of this system which, among others, led to the creation and promotion of the evidence-based principles for smoking cessation treatment, emergence of a consensus on the diagnosis and treatment of the tobacco dependence prepared by the most eminent Polish doctors [20-22], as

well as the organisation of a broad training programme on smoking cessation for healthcare professionals [65].

As part of this work, the Health Promotion Foundation (HPF), a non-governmental organization created in 1992 with the main aim on championing tobacco control activities in Poland. Amongst others, HPF has organized a competition „Quit smoking together with us” and prepared set of publications on smoking cessation treatment, including a guide “How to quit smoking. Professor Witold Zatoński advises” published in 1.5 million copies. Thanks to all these activities, Poland has become one of the leaders in tobacco control worldwide [63, 66, 67].

RECENT DEVELOPMENTS ON CYTISINE

The success of cytisine in Poland has contributed to a growing interest in this drug abroad. Professor Natalie Walker and her team at University of Auckland in New Zealand have been among a few research groups who have been recently intensely researching the effectiveness and safety of cytisine in New Zealand. The first trial conducted by her team compared cytisine with NRT (using a design similar to that of the TASK study), and provided evidence that when combined with brief behavioral stop smoking support, cytisine was superior to NRT in helping smokers quit smoking, and although it was associated with a higher frequency of self-reported side-effect, it was nonetheless safe [53, 68, 69].

Most recently, a state-private consortium Achieve Life Sciences (<https://achievelifesciences.com/>) was established in the USA to develop and research a cytisine-based drug, called “cytisinicline”. To date, Achieve Life Sciences has carried out several clinical studies, some modelled on the TASK study, to determine the efficacy and safety of the drug via a programme called Ongoing Research on Cytisinicline for Addiction, or ORCA (<http://orcaprogram.com/>). A cytisine-based drug developed by Achieve was used in a head-to-head comparative study of cytisine and varenicline (the RAURORA study), described below.

THE RAUORA STUDY

The first trial comparing cytisine with varenicline (the RAUORA study) was conducted by Professor Natalie Walker and her team [69]. The randomised double-blind trial recruited 679 patients who were randomised to receive cytisinicline or varenicline for 12 weeks. The end point of the study after 6 months is confirmed by biochemical tests for persistent nicotine abstinence. The preliminary findings from this clinical trial shows that the cytisine was more effective in quitting smoking than varenicline, as announced by Achieve Life Sciences in a report from 29 June 2020 [70]. Importantly, the study also showed that the cytisine drug showed significantly fewer side effects compared with varenicline.

The RAUROA study is now completed and awaiting publication in a peer-reviewed medical journal and should be published in the coming months. It is bringing

further evidence that cytisine-based pharmacotherapy, which has been used in Poland on a population scale and very intensively since 2000, is potentially the most effective and safe smoking cessation drug on the market. Moreover, the price of this generic is an order of magnitude smaller than that of varenicline.

It seems that the RAUORA study is another step in laying the foundations for the effective tobacco control worldwide. Cytisine is gradually becoming an “aspirin of tobacco control”. It is very popular among smokers in Poland and is being sold in millions of packages per year. Thus, it requires much greater interest from the medical community and from those responsible for public health in Poland.

CONCLUSIONS

One of the greatest public health successes in Poland since the 1990s has been a decline in tobacco-related morbidity and mortality, including from lung cancer (found among 60-80% of smokers) and cardiovascular disease (30-50% of smokers). Among the important, if not the most important factors contributing to this success have been a steady decline in smoking cigarettes among adults in Poland during this period. The availability of pharmacotherapy supporting smoking cessation, and especially of the safe and affordable cytisine-based treatment, was a key enabling factor. The popularity of cytisine has been continuously growing among smokers in Poland and remains at a high level. New developments in cytisine-based treatments and research in Poland and abroad can be further strengthen global tobacco control efforts. This warrants cytisine having much greater interest from the medical community and from those responsible for public health in Poland.

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DISCLOSURE

The authors report no conflict of interest.

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AUTHORS' CONTRIBUTION

WAZ, KJK and AH prepared the first draft of the manuscript. All authors participated in preparing the final version of the article.