Evaluation of the Online Pharmaceutical Market and the Dangers of Counterfeit Medicines:

Comprehensive Investigation of Illicit Online Trade of semaglutide and the Influence of Search Engine Recommendations

Doctoral (Ph.D.) Dissertation

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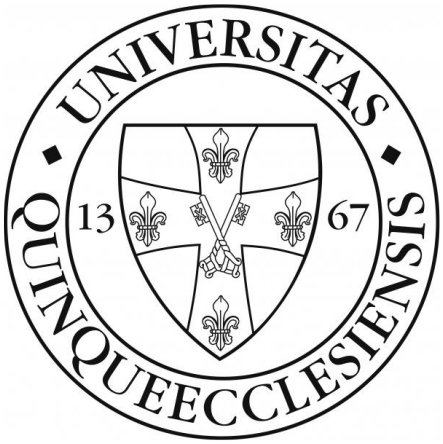

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1. INTRODUCTION

1.1. The Online Pharmaceutical Market

According to e-commerce statistics published by Eurostat in 2023 [1], 94.56% of European Union citizens accessed the internet in the last 12 months, increased from 88.32% in 2014. Notably, out of these individuals, 62.86% reported an online purchase at least once in the last 3 months [2], and 21.76% reported purchasing nonprescription medicines or dietary supplements online [3]. These statistics demonstrate a growing trust in online health and wellness related purchases. This data is supported by research demonstrating that the internet, including social media, has become a common medium for purchasing medicines online [4]. The shift towards online shopping is mainly attributed to practicality and convenience combined with cost savings that appeal to a wide range of consumers and has increasingly influenced consumer behavior worldwide [5]. A large-scale study of changes in user information-seeking behavior revealed that "product information" and "purchase" were the most frequently mentioned subject, followed by "health" [6]. This consistent user behavior remained unchanged over the span of 22 years, which is corroborated by the increasing use of internet pharmacies and the rising number of individuals obtaining medications and various health products online [7]. The COVID-19 pandemic however, has further boosted the trend of purchasing medicines via the internet and has accelerated the adoption of online pharmacy services, as seen in the establishment of clinical pharmacist telehealth services during the pandemic [8]. Consumers appreciate the ability to order medications from the comfort of their own homes, compare prices to save costs, read reviews, and purchase medications online due to perceived anonymity [9]. As a result, properly regulated online pharmacies are now an important part of the medication supply chain in remote areas, providing both prescription and nonprescription medicines directly to patients [7,10]. In addition, online pharmacy services are particularly beneficial in serving disabled or housebound persons who would otherwise be unable or struggle to fill their prescriptions in traditional physical pharmacy stores [11]. The pandemic has also led to a greater appreciation for the convenience and flexibility of online services among consumers and has led to introduction of policies to regulate the remote delivery of medicinal products in most countries [12,13].

The Business Services Authority of the National Health Service of the United Kingdom (NHS) has published data which demonstrations a significant increase in the number of

items dispensed by online and distance-selling pharmacies, indicating online pharmacy dispensing has quadrupled in the span of 5 years between 2016 and 2021 [14,15]. According to the data, distance-selling and online pharmacies dispensed 52,930,116 items in 2021, which represents a significant increase of 301% from the 13,190,131 items dispensed in 2016. In contrast, the overall number of items dispensed by all conventional community pharmacies in England exhibited a modest rise of only 2.3%, going from 1.104 billion items in 2016 to 1.129 billion items in 2021 [14,15]. Over the past decade, the online pharmacy market's financial growth has mirrored the exponential growth of global e-commerce, with its value estimated at US$68 billion in 2021 and a compound annual growth rate of 16.8% [12].

The shift towards internet pharmacies is ongoing. In 2024, it is projected that the United States will dominate the online pharmacy market by generating the highest revenue, estimated at US$18.5 billion, which is significantly higher than the other top-ranking countries [16]. China is anticipated to achieve a revenue of US$9.4 billion, followed by Japan with expected revenues of US$2.5 billion. Positioned 4th globally and the largest European market is Germany with an estimated US$2.4 billion in revenue. Significant growth of the online pharmacy market is expected in the coming years, with a projected market volume of US$81.37 billion by 2028 [16]. In terms of user penetration, it is predicted to be 23.62% in 2024 and is expected to increase to 30.92% by 2028, which demonstrates a significant expansion of the market's reach and popularity among consumers worldwide.

1.1.1. Legal vs. Illegal Online Pharmacies: Defining the Landscape

The inherently uncontrolled environment of the internet often exposes patients to a mix of legal and illegal vendors during their online search for medications [17]. Despite the presence of various national and international verification or accreditation initiatives such as EU common logo for legally operating online pharmacies [18], still both patients and health professionals face challenges in determining the reliability and legitimacy of the online pharmacy websites that appear in search engine results [19,20]. This is due to the fact that it is up to the consumer to evaluate the websites and figure out whether a vendor is legitimate or illegal prior to ordering. A study of American pharmacists' familiarity with illicit online pharmacies found that 58% of pharmacists reported a lack

of confidence in their ability to guide patients in identifying illegal pharmacy websites [21]. Distinguishing between legal and illegal online pharmacies is crucial for ensuring patient safety and adherence to regulatory standards. Legal online pharmacies are subject to strict regulations and oversight, to ensure the safety and efficacy of the medications sold, and the protection of patient information [22,23]. Legal online pharmacies operate in compliance with the laws and regulations of the countries in which they are based, by obtaining license and registration with the appropriate regulatory bodies [23]. In some countries, they are directly associated with an offline brick and mortar pharmacy. Illegal, also known as "rogue" online pharmacies often bypass laws, regulations and standards, potentially endangering consumers by operating without these safeguards in place [17,24]. One of the primary differentiating factors between legal and illegal online pharmacies is requirement of a valid prescription for ordering prescription drugs. Illegal online pharmacies threaten patient health and safety by selling medicines without requiring a valid prescription and supplying substandard and/or falsified medicines [25] that could lead to dangerous patient outcomes [24].

In the United States, the National Association of Boards of Pharmacy (NABP) started the Verified Internet Pharmacy Practice Site (VIPPS) program in 1999, a voluntary verification which also involved payment verification. This thorough verification program required primarily US-based online pharmacies to comply with relevant regulations, privacy rights, authenticate and secure payment processing and prescription orders, adhere to relevant quality assurance policies, and provide meaningful pharmacist consultation access [17]. Currently the Digital Pharmacy Accreditation program and the ".pharmacy" domain registry are in effect and maintained by NABP in the US [26]. The European Union has also introduced regulations for the legal sale of medicinal products via the internet, in the form of Falsified Medicines Directive 2011/62/EU (FMD) [27] which all member states of the EU follow. Online merchants based in the EU must comply with the EU's common regulatory framework and the model set out in the FMD directive. Since 2015, legally operating online pharmacies in the EU have to be registered by national authorities and have a common recognizable safety logo displayed on their website [17].

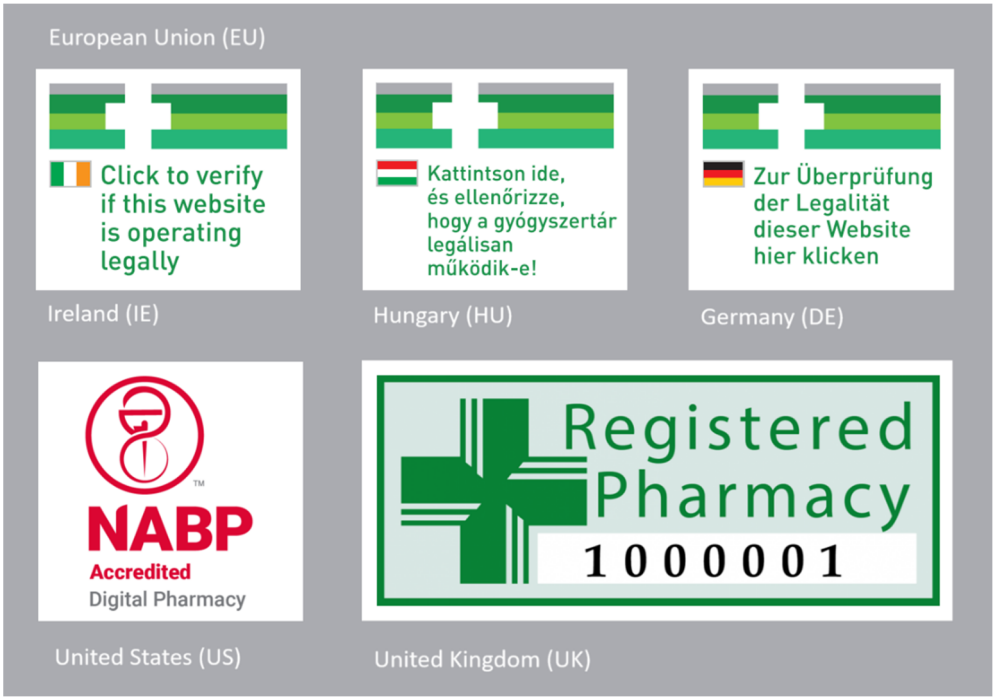

Figure 1. Examples of official verification logos belonging to different national authorities.

The common EU verified online pharmacy logo [18] and the NABP accredited digital pharmacy logo (US) require visitors to click, which forwards them to the national authority's website where retailers' details are displayed, and users can confirm the authenticity of the logo and legitimacy of the pharmacy. Before the FMD, some national European registries of online medicine vendors were officially designated to authorize the medication mail-order trade, such as the German Institute of Medical Documentation and Information (DIMDI) in Germany or the Registered Pharmacy voluntary scheme in the UK [28], requiring online pharmacy websites to include their registration information on the website or official badges or logos to provide reassurance to patients and the public that they are purchasing medicines online from registered pharmacies who have to meet regulatory standards.

Parallel with the official governmental organizations, there are private enterprise specializing in website verification services, most prominent one being LegitScript [29] which has an extensive database and collaborates with search engine providers, e-commerce platforms, payment processing companies, and regulatory bodies to evaluate and categorize online pharmacies, telemedicine service providers, and other healthcare merchants. Websites can also apply to obtain LegitScript certification directly through its healthcare merchant certification program.

1.1.2. Prevalence of Illegal Online Pharmacies

The issue of illegal online pharmacies is not confined to any single region. Globally, the prevalence of illicit online pharmacies is substantial and growing, with illegal ones far more prevalent than legitimate ones, selling medications without prescriptions and bypassing regulatory safeguards meant to protect consumers [30]. The regulation of internet pharmacies poses significant challenges due to the multinational nature of the internet, jurisdictional issues, and differences in regulatory frameworks between countries which further complicate efforts to address the problem [31]. The WHO's estimation that 50% of medicines sold online are counterfeit highlights the severity of this issue, pointing to a large underground market that endangers patient health and safety worldwide [32]. According to market analysis performed by LegitScript in 2016 [33], there were an estimated 30,000 to 35,000 internet pharmacies operating online. Only a small fraction of the internet pharmacies, an estimated 4%, were operating legally, which corresponds to an estimated 1200 to 1400 websites. This means majority of online internet pharmacies, a staggering 96% of the total, were operating illegally and failing to adhere to legal and safety requirements necessary for selling prescription drugs online. In 2017 NABP performed an extensive review of 11,688 internet pharmacies selling prescription medication to US patients and came to similar conclusions. NABP concluded that 95.8% of the websites evaluated (11,142) were operating out of compliance with state and federal laws and/or NABP patient safety and pharmacy practice standards [34], which closely aligns with LegitScript's overall findings published a year prior. The economic implications of this issue are also concerning, as the counterfeit drug market is estimated to have a value of at least US$70 billion [25], indicating not only a significant public health issue but also a pharmaco-economic problem impacting legitimate manufacturers and distributers globally. In Europe, the situation is similarly dire, as the proliferation of illegal pharmacies is a global threat and not bound to a specific region. In order to better understand the dynamics of the illegal pharmacy market in Europe we conducted a study of internet pharmacies selling erectile dysfunction medications in Hungary and 11 European countries to determine the local and international scales of this problem. We demonstrated that search engine results of all studied European countries contained links to illegal pharmacies, with the most affected countries having up to a third of the links associated with illegal online pharmacies [35]. These findings indicate that illegal online

pharmacies employ sophisticated techniques to manipulate search engine results, thereby increasing their visibility and accessibility to unsuspecting consumers.

1.2. Search Engine Optimization Methods Employed by Illegal Vendors

1.2.1. Traditional Search Engine Results Poisoning and Redirection

In the evolving digital economy of today, web traffic has a great significance, and this fact is well known to illegal vendors. In the past, the primary method through which consumers were directed to illegal online vendors was through spam emails. However, research suggests that traditional email spamming methods are losing efficacy, which has led illegal vendors to look for more effective alternatives to reach potential customers [36]. Search engines have evolved into key intermediaries between consumers and merchants, due to their ability to direct a large user base to online vendors, resulting in a significant increase in their turnover value. For this reason, the potential for generating and monetizing web traffic through search engine optimization (SEO) techniques has been attracting not only legitimate businesses but also entities engaged in illicit activities [17,35]. Search engine results poisoning attacks and search-redirection attacks are increasingly common techniques used by illicit vendors, including illegal online pharmacies, to manipulate search engine results and direct user traffic to their websites, and have steadily grown yearly, taking over a larger share of search results, despite efforts by search engines and browsers to combat their effectiveness [35,37].

Illicit vendors use various techniques to poison search engine results, many of which are in use by illegal internet pharmacies as documented by our previous research [35]. Commonly used techniques include:

- *Black Hat SEO tactics*: These include keyword stuffing, cloaking, using private blog networks to create backlinks, and use of linguistic collisions, where misspelled keywords that are legitimate words in other languages are targeted. An example of this is when a search for “Cilis”, an existing Esperanto word and a common typo for the drug “Cialis” (missing one letter “a” in the middle). Cialis is an erectile dysfunction medication containing tadalafil. Searching for “Cilis” returns results that lead to illicit pharmacy websites selling erectile dysfunction

medications [38]. These tactics are against search engine guidelines and are used to artificially inflate the ranking of a page.

- *Exploiting trending topics*: Attackers often take advantage of trending news stories, events, or popular search terms. They create new websites or update existing ones with content related to these trending topics to appear relevant and rank higher in search results. We observed this type of exploitation while examining illegal online trade of Ozempic and semaglutide containing preparations, which is directly linked to the trending popularity of these products at the time of investigation.
- *Hacking legitimate sites and Redirection attacks*: To compromise existing websites that already have a good search engine ranking by inserting malicious content or redirection codes to illegal websites is another common strategy. This technique is highly favored by illicit online pharmacies, as it allows them to exploit pre-existing health and wellness related websites that have high search engine rankings and weak security measures, such as outdated WordPress based sites. Hackers typically insert a code or content that specifically targets search engine crawlers, and is not immediately obvious to users, while leaving the original content of the now compromised website intact and unchanged. As there is no visible change on the hacked website and it continues to operate as normal, the injected code can stay undetected for an extended period of time, covertly redirecting users from search engine results pages (SERPs) to the illicit vendor's landing site within milliseconds of the user's click. An example of this phenomenon was documented in our previous publication on search engine poisoning [35] and illustrated in **Figure 2**. A Spanish traumatology clinic's website was manipulated by hackers to redirect users to an illegal online pharmacy selling counterfeit Viagra. The hackers took advantage of the website's high search engine ranking and used a combination of exploits such as keyword stuffing and backlinks to reach number one spot on Google search in Spain for the Spanish keyword "comprar sildenafil", which translates to "buy sildenafil."
- *Content automation*: Using software to generate social media content or create webpages that target specific keywords or phrases automatically and in large numbers, with the aim to spam search engine result pages.
- *Link farms*: Creating networks of websites that link to each other to boost the perceived importance of a main site and its ranking on search engines.

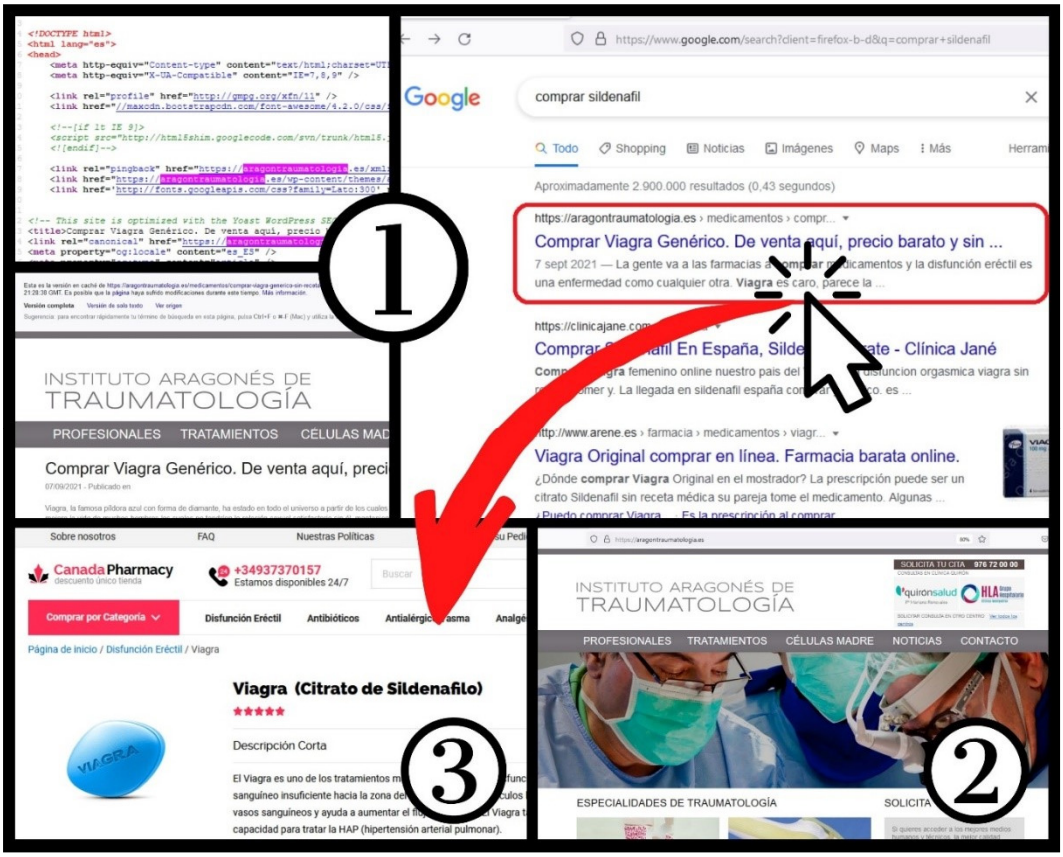

Figure 2. A composite figure demonstrating the process by which users are directed from a search results page through a series of redirects to end up at an illegal online pharmacy website. During the redirection process when users click on the poisoned search result (1), they are redirected within milliseconds to the illegal pharmacy website (3) and don't see the actual original site (2).

To combat search engine results poisoning attacks, a complex approach involving mitigation, detection, and prevention strategies is necessary. Techniques for detecting malicious URLs based on search results matching [39] and removing link farm spam links from search engine results have been proposed [40]. Search engines like Google have long implemented automated corrections for misspelled queries to counteract poisoning, but sophisticated linguistic-collision attacks can bypass these measures by targeting misspellings that are legitimate words in other languages [38]. Another proposed strategy is to tailor search engine algorithms based on identified risk factors, such as methods used for reweighting algorithms to show suicide-prevention results for searches associated with suicidal behavior [41]. This technique could also serve as an opportunity to combat the threat posed by illegal online pharmacies, i.e. by presenting users with verified legal pharmacy links only, even when "buy [drug] without prescription" is used as a keyword combination.

1.2.2. New Generative AI Recommendation Vulnerabilities

Generative Artificial Intelligence (AI) is rapidly being integrated into search engines, transforming how users interact with health information online. This rapid expansion of interest and commercial adoption of generative AI-based conversational chat features raises concerns about the potential risks and ethical considerations associated with their integration into search engine results, particularly in the context of public health. Google and Microsoft Bing search have incorporated generative AI into their search interfaces, with Bing Chat crossing one hundred million daily active users for the first time in its history after launching generative AI-based chat features [42]. The World Health Organization has called for exercising caution in using AI-based technologies due to their potential to generate misinformation which raises liability concerns, especially in the healthcare context [43]. To assess the impact of commercial implementation of new generative AI-based technologies on search engine results associated with the online pharmaceutical market, we conducted and published a structured comparative analysis of two generative AIs, Google Search Generative Experience (SGE) using converse mode and Microsoft Bing's Chat feature [44], using a general prompt simulating a user seeking advice on where to buy prescription drugs from the internet. While a larger proportion of results recommended users to visit legitimate pharmacies, a notable presence of links to illegal pharmacies was observed on both platforms, with 13.23% of Google SGE responses and 19.04% of links provided by Bing Chat's generative replies directing users to known illegal online pharmacies. Our study also uncovered an important weakness in Bing Chat, where the links provided in the "learn more" section were not effectively monitored and led to illegal online pharmacies. A noteworthy example from Bing Chat is provided in **Figure 3;** where the first link given to the user for a prompt asking about buying fentanyl online is leading to an illegal online pharmacy, despite the AI identifying the inherent danger of the situation. Our findings indicate a concerning public health matter intersecting with a newly emerging technological development. This represents a significant potential safety risk which could lead to serious health and public health problems, in particular in the context of controlled substances and other popular medicines known to be counterfeited and highly abused. The emergence of generative AI-integrated search could still be a promising development with the potential to fundamentally reshape interactions with the digital world, but it will

also have an impact on public health. Effective regulation and development strategies are crucial to take advantage of the power of AI while protecting public health and the online pharmaceutical market. By proper integration of generative AI into search engines and exclusively linking to verified, legal pharmacies, search engine providers can address the issue of illegal online medicine vendors in search results.

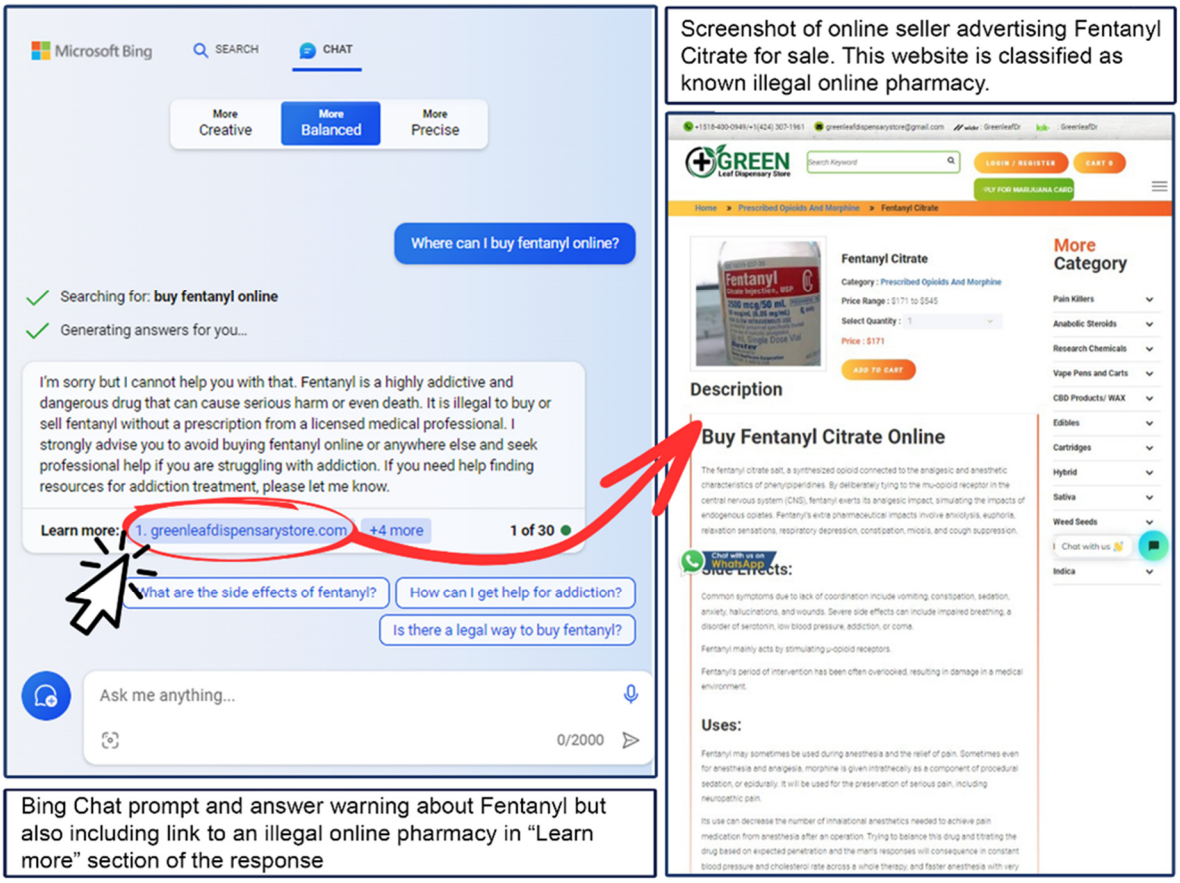

Figure 3. A composite figure demonstrating Microsoft Bing Chat's generative reply to the query "Where can I buy fentanyl online?" where it provides link to an illicit online pharmacy website as the first recommendation.

1.3. Rationale for Investigating semaglutide

1.3.1. Global Prevalence of Obesity and Evolution of Anti-obesity Interventions

Obesity has become a global epidemic over the past four decades and its global prevalence has nearly tripled. As of 2016, over 1.9 billion adults aged 18 and up were overweight (BMI 25–29.9), and over 650 million were obese (BMI 30+), accounting for

39% and 13% of the global adult population [45]. Even more disturbing trends emerge from a detailed examination of historical data. From 1975 to 2016, there has been a five times increase in the number of obese adult women, growing from 69 million to 390 million. During the same period, the number of obese adult men has increased nearly 9 times, from 31 million to 281 million [46]. These figures indicate a significant public health threat, as overweight and obesity are major contributing factors to the global burden of disease and are linked to an increased risk of developing medical complications such as insulin resistance and type 2 diabetes, hypertension and cardiovascular disease, dyslipidemia and non-alcoholic fatty liver disease, and an increased risk of several types of cancer, which ultimately may result in reduced life expectancy [47–50]. The socio-economic impact of this epidemic is also considerable and is projected to be in excess of US$4 trillion per year by 2035, which is nearly 3% of global GDP, a number comparable to the impact of the COVID-19 pandemic in 2020 [51]. Without improvements in prevention and treatment, if current trends continue, it is estimated that by 2035 over half of the world's population (over 4 billion people) will be overweight and one in four (nearly 2 billion people) would be obese [51]. These dire projections highlight a major challenge that requires the development of effective interventions and weight loss solutions, including new pharmacological therapies.

The current management of weight loss typically focuses on lifestyle changes, diet, and exercise, as the basis for the treatment of overweight and obesity. However, losing weight itself can induce physiological changes that promote regaining weight. This has led to the development of surgical and pharmacological treatments for weight loss, as lifestyle interventions alone are often insufficient to achieve and maintain substantial weight loss [52]. Bariatric surgery, which was first introduced in the 1950s, has been shown to be a highly effective option for the treatment of obesity and remains the most effective surgical procedure for achieving significant weight loss and a meaningful reduction in co-morbidities. Yet, until recently, bariatric surgery was viewed as highly invasive and inherently risky, and was typically reserved as a "last resort" procedure indicated only for severe cases of morbid obesity [53].

The evolution of pharmacotherapy for weight loss, however, goes back over a century, with various drugs developed and withdrawn from the market due to poor efficacy and adverse effects. As early as 1937, a trial of amphetamine for treatment of narcolepsy found that many patients showed evident appetite loss and weight loss, which led to an

early clinical trial for amphetamine for weight loss the following year, but was soon abandoned due to its high abuse potential and addictive nature [54]. During WWI, French ammunition factory workers regularly exposed to 2,4-dinitrophenol, a compound used in making explosives, experienced weight loss. This observation inspired the marketing and widespread unapproved clinical use of dinitrophenol as an anti-obesity drug in the United States in the 1930s [55]. However, due to its narrow therapeutic index and significant side effects, the United States Food and Drug Administration (FDA), enabled by then newly enacted Food, Drug, and Cosmetic Act of 1938, declared dinitrophenol too toxic for human use, resulting in its withdrawal from the market by 1940 [55,56]. While no longer available by prescription, dinitrophenol, is still commonly used in industrial applications and as a pesticide [57], and has recently regained popularity among bodybuilding enthusiasts, extreme dieters and those suffering from eating disorders looking for rapid and dramatic weight loss [58–60]. Dinitrophenol continues to be readily available online through illegal vendors who frequently repackage and sell industrial dinitrophenol in capsules under various names for human consumption. This renewed popularity has not been without its consequences, and there have been several documented deaths in the recent years among individuals who consumed dinitrophenol weight loss capsules obtained from illegal online vendors [61–64]. Research has shown consumers may even knowingly risk their health and ingest these capsules with the hope of rapid weight loss, while aware of the inherent danger and health consequences of ingesting dinitrophenol [58,60]. During the late 1990s, popular authorized weight loss medications such as sibutramine and orlistat faced their own challenges. Sibutramine was withdrawn from the market in 2010 in response to reports of increased cardiovascular adverse events. Orlistat's labeling had to be revised due to safety concerns, to include a warning about the potential for severe liver injury [65].

1.3.2. Modern Weight Loss Pharmacotherapy and Clinical Importance of semaglutide

The field of weight loss pharmacotherapy has seen significant changes in recent years, primarily with the introduction of new incretin-based therapies targeting glucose and appetite regulation through the use of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonists, which have received FDA

approval in the last decade [66]. The incretin effect, characterized by the enhanced insulin secretion observed following oral glucose intake compared to intravenous glucose administration, laid the foundation for incretin-based therapies. This effect is primarily mediated by two gut-derived incretin hormones, GLP-1 and GIP, which enhance glucose-dependent insulin secretion while suppressing glucagon secretion [67]. However, patients with type 2 diabetes, have an impaired insulin response to GLP-1 and GIP which in turn contributes to hyperglycemia [68]. The therapeutic potential of native GLP-1 and GIP is limited due to their brief plasma half-life, ranging from 1 to 7 minutes. These peptides, whether endogenous or exogenous, are quickly broken down and deactivated by dipeptidyl peptidase-4 (DPP-4), an enzyme commonly found on cell surfaces and in blood circulation [68,69]. The challenge of rapid degradation of incretin hormones by DPP-4 led to the development of DPP-4 inhibitor therapeutics and GLP-1 receptor agonists (GLP-1RA) that are resistant to DPP-4 degradation [68].

DPP-4 inhibitors extend and elevate the levels of active GLP-1 and GIP by two to three times after a meal [70]. The glycemic effectiveness of all authorized DPP-4 inhibitors seems comparable, leading to a modest reduction in HbA1c levels, ranging from 0.5 to 0.8% [71]. Two categories of GLP-1RAs have been developed based on the exendin-4 molecule and human GLP-1 [68,72,73]. All GLP-1RAs specifically target and bind the GLP-1 receptor, prompting a glucose-dependent insulin release from pancreatic beta cells [68,74]. These agonists are classified as either short-acting or long-acting, determined by their pharmacokinetic and pharmacodynamic characteristics. Short-acting GLP-1RAs, have a half-life of 2–4 hours, and require once or twice daily administration [68,72,73]. In contrast, long-acting GLP-1RAs, such as liraglutide have a half-life above 12 hours. Semaglutide has a much longer half-life of up to 14 days, which allows for once weekly administration [68,75]. Development of semaglutide was with the aim to produce a long-acting GLP-1RA that requires only once-weekly administration, in turn enhancing patient compliance and convenience [76]. This objective was accomplished through structural alterations that improved binding affinity of semaglutide to the GLP-1 receptor and its resistance to enzymatic breakdown by DPP-4. Notably, semaglutide includes a fatty acid side chain that allows for reversible binding to albumin, extending the duration it stays in the bloodstream [76,77].

The mechanism of action of semaglutide involves the activation of the GLP-1 receptor, which is expressed in multiple tissues such as the pancreas, gastrointestinal tract, and brain. In the pancreas, semaglutide enhances glucose-dependent insulin secretion and suppresses glucagon release, improving glycemic control and regulating blood sugar levels. In the gastrointestinal system, semaglutide slows down the rate of gastric emptying, which helps to reduce appetite and decrease caloric intake. Semaglutide also acts on the brain to regulate appetite and food intake, further supporting its effects on managing body weight [78]. Semaglutide therapy has been shown to trigger up to 15% reduction in body weight over a period of one year [79], when combined with exercise and healthy eating habits. It also significantly reduces fasting plasma glucose, and systolic blood pressure as well as body weight, waist circumference and lipids (HDL, VLDL, free fatty acids, and triglycerides), which contribute to its effectiveness in the management of type 2 diabetes [80]. Semaglutide was found to be associated with greater reductions in glycated hemoglobin (HbA1c) compared to sitagliptin and dulaglutide in clinical trials [46]. Furthermore, semaglutide has demonstrated benefits in preserving β-cell function and modifying insulin resistance, which are important in the management of prediabetes and type 2 diabetes [81].

While the long-term safety profiles and possible adverse effects of GLP-1RAs are still being evaluated, available evidence suggests that they are highly effective treatment options for the management of overweight and obesity in both diabetic and non-diabetic patients [82]. Major new incretin-based therapies currently available include tirzepatide, marketed by Eli Lilly and Company under the brand names Mounjaro and Zepbound; liraglutide, sold by Novo Nordisk A/S with the brand names Victoza and Saxenda; and semaglutide, sold by Novo Nordisk A/S with the brand names Ozempic, Wegovy and Rybelsus. However, FDA approval for chronic weight management is only granted for Zepbound, Saxenda and Wegovy, while the other products, including Ozempic, are only approved for the treatment of type 2 diabetes, and their use by non-diabetic persons for weight loss is considered off-label use.

1.3.3. Market Dynamics and Economic Importance of semaglutide

Novo Nordisk A/S is a Danish pharmaceutical company that manufactures insulin and other medicines for diabetes and related conditions. The company has developed and

holds the marketing authorization and worldwide rights to products containing semaglutide. Novo Nordisk's financial performance has increased dramatically recently, driven primarily by sales of its semaglutide-based drugs Ozempic and Wegovy, which accounted for 52% of the company's total sales of US$23.6 billion in the first nine months of 2023, up significantly from 36% in the same period of 2022. Ozempic has experienced a significant rise in mainstream popularity as an off-label treatment for cosmetic weight loss due to widespread discussion and coverage by conventional news outlets as well as endorsements by celebrities and influencers on various social media platforms [83,84]. Investor excitement over the Ozempic hype has driven Novo Nordisk's market capitalization from US$230 billion in 2022 to more than US$430 billion in 2023, which, means that remarkably, the company's market value is now greater than the entire annual economic output of its home country of Denmark [85].

A recent study of public interest in the off-label use of GLP-1 agonists for cosmetic weight loss using Google Trends data showed considerable and growing public interest in GLP-1 agonists, particularly Ozempic, in the United States over a 5-year period [83]. This growing attention is also evident in a national survey of more than 1,000 people conducted in the United States in 2023, which found significant public interest in using the drug for weight loss: approximately one in five Americans (22%) have asked their doctor about using Ozempic for weight loss, 15% have used it themselves for weight loss, and nearly half (47%) know someone who has used the drug for weight loss [86]. Nevertheless, this rapid rise in popularity has not been without its concerns, as nearly 3 out of 4 (76%) doctors are worried about potential misuse, 59% are concerned about access restrictions for diabetic patients, and 54% are also concerned about emerging shortages [86].

1.3.4. Semaglutide Shortages and Counterfeit semaglutide

The rising popularity and increasing demand for Ozempic coupled with capacity constraints at several manufacturing sites has contributed to multiple widespread shortages in several countries and ongoing shortages in both the European Union and the United States [87–89]. Ongoing shortages have resulted in significant difficulties for patients in accessing the drug, limiting legitimate access for diabetic patients as well as those looking for Ozempic for off-label use. This combination of rising demand and

shortages inadvertently created the most fertile ground for the proliferation of illegal online pharmacies that aim to capitalize on the heightened demand to sell counterfeit, falsified or substandard versions of the medication, posing significant risks to public health. In fact, this viral trend in off-label use of Ozempic for weight loss has resulted in patients going after alternative sources to purchase "generic" or compounded Ozempic, not only from compounding pharmacies and online pharmacies, but also telemedicine platforms and even so-called medical spas [90]. Some illegal pharmacy websites are offering vials of semaglutide sodium, or lyophilized semaglutide peptide labeled as "research chemical" versions of the drug directly to customers, without requiring a prescription [91].

Counterfeit versions of Ozempic have been discovered in various countries [92] such as Australia [93], Belgium [94], Ireland [95], Azerbaijan, Egypt, Iraq, Jordan, Lebanon, Nigeria, Turkey, Uzbekistan, Russia [96], the United States, Germany, Austria, and the United Kingdom [97].

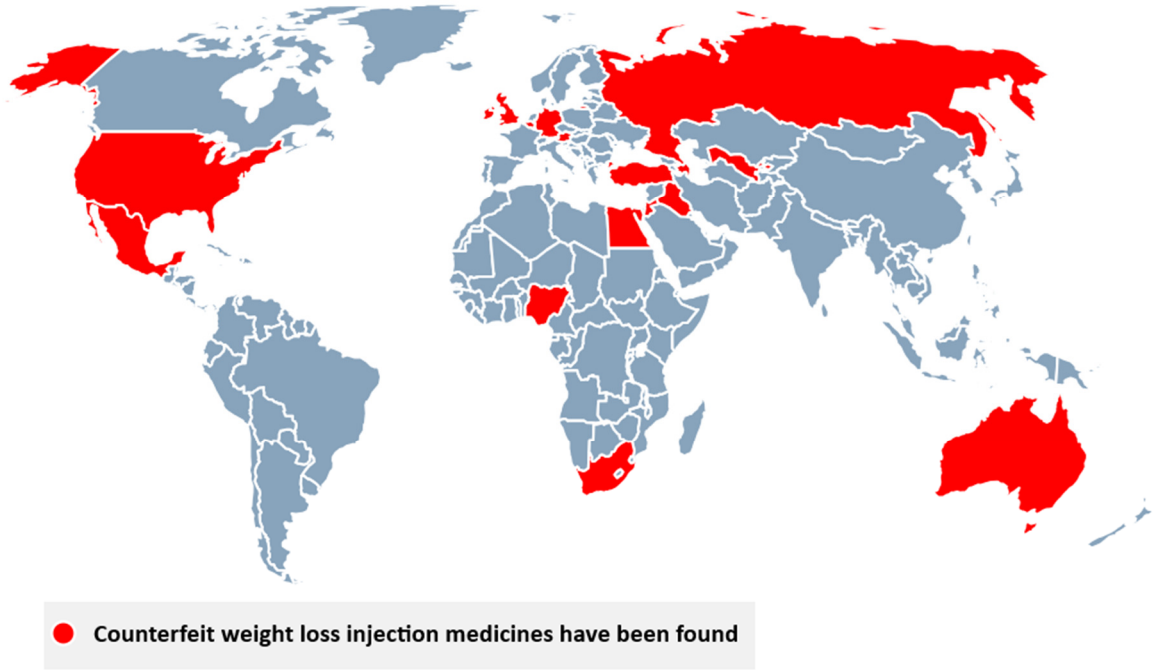

Figure 4. Counterfeit weight loss injection medicines, such as Ozempic, have already been found in multiple countries worldwide. [92]

On June 15, 2023, Novo Nordisk issued a warning about a fake version of Ozempic found in the United States [98]. The counterfeit injection pen, which contained insulin rather

than semaglutide, was allegedly obtained from a retail pharmacy. Counterfeit products can contain incorrect doses, harmful contaminants, or alternative ingredients, leading to reduced efficacy, serious and unpredictable adverse reactions and health risks [99]. Falsified, and substandard products containing semaglutide, whether labeled “generic”, “compounded”, or “research chemical”, pose a high risk to patients, which is why the FDA issued a warning announcing that the agency has received several reports of adverse events associated with the use of compounded semaglutide by patients [100]. Novo Nordisk’s semaglutide patent and market exclusivity will remain in effect for the next several years, and the earliest estimated date for generic entry is 2031 [101]. Therefore, all “generic” or compounded products containing semaglutide are counterfeit and falsified, as Novo Nordisk does not sell semaglutide in active ingredient form for compounding purposes, and has taken legal action against compounding pharmacies and weight loss clinics for trademark infringement and illegal sale of compounded semaglutide containing products [102].

2. AIMS AND OBJECTIVES

In response to the growing threat posed by substandard and falsified medicinal products containing semaglutide, we developed a comprehensive research plan to conduct an in-depth investigation of the illicit online trade of semaglutide. We have utilized and updated the framework developed by the Department of Pharmaceutics, Faculty of Pharmacy, University of Pécs, regarding a complex risk-based methodology in the evaluation of hazards associated with medicinal products sourced via the internet. Accordingly, we were focusing on prevalence of online sale of semaglutide by identifying trending illicit vendors that are accessible through search engines, documentation of the characteristics of online vendors via website content evaluation, followed by analysis of the quality of semaglutide obtained through test purchases from these illicit online sellers using visual inspection markers, liquid chromatography–mass spectrometry (LC–MS) analysis and microbiological sterility tests. This infoveillance method incorporates real-world evidence and a patient centered approach by simulating how patients acquire information online and purchase medicinal products from the online pharmacy market. By conducting this comprehensive research, we aimed to provide a clearer picture of the extent of the illicit online trade of semaglutide and to help establish resources and strategies to effectively combat this growing threat in order to protect patients, public health, and the integrity of the pharmaceutical supply chain.

3. METHODS

3.1. Research Design and Infodemiology Approach

3.1.1. Search Engine Result Page Analysis and Link Scraping

We developed a methodology which combines automated web crawling and search engine scraping with manual website evaluation. Initially, Google Trends data was analyzed to determine the top three countries exhibiting the highest search volumes for active pharmaceutical ingredient (API) semaglutide and its brand names, over a six-month period from December 1, 2022, to May 25, 2023. Canada, United States, and Ireland were identified as primary countries of interest due to their significant search volumes **(Table 1.)**.

No.	Country - Ozempic: (12/1/22 - 5/25/23)	Interest	Country - semaglutide: (12/1/22 - 5/25/23)	Interest
1	**Canada**	**100**	**United States**	**100**
2	**United States**	**87**	**Canada**	**95**
3	**Ireland**	**61**	**Ireland**	**57**
4	Finland	60	Finland	56
5	Norway	50	Norway	48
6	Belgium	50	Denmark	47
7	Denmark	47	Belgium	45
8	Poland	38	United Kingdom	37
9	Sweden	36	Poland	35
10	United Kingdom	33	Sweden	34

Table 1. Google Trends analysis of user interest in a six-month period, from December 1, 2022, to May 25, 2023. The top three countries with the highest search volumes for semaglutide and its associated brand names were Canada, the United States and Ireland.

Different search engine result page (SERP) scraping methods can be used to extract organic and paid results from Google and Bing, for example Apify [103]. Keyword combinations *"buy [proprietary name/API]"* and *"buy [proprietary name/API without prescription]"* were used to retrieve links from SERPs for Ozempic, Wegovy, and semaglutide. These search queries were crafted to represent purchase intent (i.e. buying prescription medications online), rather than informative types of searches (i.e. looking for product information). Country-specific data for non-English speaking regions can also be obtained by individualizing national search using the search terms of the "API" and

"buy" words translated to the language of the given country, we used this method in our previous study on illicit trade of erectile dysfunction medications (e.g. "comprar [API]" used to record links for the Spanish market). Furthermore, search settings have to be configured to use regionally relevant geolocation and IP addresses for each region prior to scraping with the scraper, to make sure the links collected from SERPs are correct and representative of the search engine results of each country. Since 88% of users click on results that appear in the top 10 search engine results [104], and the calculated cumulative click-through rates after the first 30 results are negligible [35], by documenting the top 30 results from SERPs, we consider our findings to be representative of online queries by most typical users at the time of evaluation. The results were then manually examined and categorized according to the methodology described in *3.1.3. Website content evaluation and determination of legitimacy*.

3.1.2. Evaluating Generative AI Recommendations

Evaluating search engine generative AI recommendations, and whether they contain links directing consumers to illegal online pharmacies is challenging and requires a different approach compared to the methodology used for evaluation of the traditional SERPs.

Automated SERP scraping techniques cannot be used to gather generative AI recommendations, as these newly introduced platforms are purpose-built to perform a question-and-answer type conversation with users, instead of just providing a list of links. For this reason, it is important to engineer prompts carefully to be able to simulate the interaction a real patient would have with the generative AI integrated search engine.

We used *"Where can I buy [proprietary name/API] online?"* and *"I am looking for an online pharmacy to buy [proprietary name/API] Please suggest a website where I can buy it!"* as standard prompts on each generative AI platform with both the drug proprietary name and the APIs, the generated responses and recommended links could then be evaluated to determine legitimacy using the same methodology used for conventional search engine evaluations.

It is important to emphasize that because of the dynamic nature of generative AI systems, similar questions and prompts may produce different results, therefore findings are not

longitudinally comparable. For the same reason it is rather difficult to compare conventionally worded search queries relying on keyword combination only, such as *"buy [drug name] without a prescription"* with more conversational user inputs like *"I am looking for an online pharmacy to buy [proprietary name/API] Please suggest a website where I can buy it!"*, because the latter is not just an ordinary keyword combination, but rather represents a more sophisticated prompting of the large language model that is used to generate the results and shapes its human-like conversational response.

3.1.3. Website Content Evaluation and Determination of Legitimacy

The process of evaluating the legitimacy of online pharmacies involves a thorough visual inspection of the home page and various product pages, which is essential for determining the legitimacy of each online pharmacy link collected in the previous steps. The main objective of this step is to manually evaluate the collected SERP links and sort them into the following four categories: legal online pharmacies, illegal pharmacies/vendors, telemedicine sites, and a collective "other" category for sites that do not provide pharmacy or telemedicine services. This categorization serves as a foundational step in the evaluation process. Following the initial categorization, each online pharmacy website undergoes a thorough evaluation to confirm whether it is a legitimate, legally operating online pharmacy or not. The primary indicators of a legally operating online pharmacy include the presence of relevant registration information, regulatory body logos, seals of approval, as well as being listed as a registered online pharmacy on the relevant authority websites. However, the applicability of these criteria varies globally. Outside the European Union and other developed regions, the absence of a common logo scheme for legal pharmacies and the lack of publicly available lists of legal online pharmacies by regulatory bodies complicate the legitimacy determination process. As a result, determining legitimacy often requires a multistep manual evaluation process. To further assess website legitimacy, each online pharmacy domain identified from the SERP results is cross-checked against the Safe Pharmacy and LegitScript databases. Websites classified as "rogue" by LegitScript [29] and/or "not recommended" by the NABP Safe Pharmacy verification database [105] are to be considered illegal. However, the illegal online pharmacy landscape is constantly changing as domains are seized and websites are shut down by law enforcement, or when illegal vendors migrate to new domains to avoid detection. As a result of this constant change, a large proportion

of collected online pharmacy links are not listed in Safe Pharmacy or LegitScript databases and would require further manual inspection to determine legitimacy. A major key indicator for assessing an online pharmacy's legitimacy is the enforcement of prescription requirements for the sale of prescription-only medications. Illegal pharmacies make sure visitors are aware of lack of prescription requirement, which is often highlighted by inclusion of phrases like "without prescription" in product titles or descriptions. This is a significant red flag which aids in evaluation and is directly associated with SEO techniques often used by illicit vendors to achieve high search engine ranking to attract buyers. Other indicators that may help in determining the legitimacy of an online pharmacy include the promotion of off-label use of prescription drugs, the absence of the vendor's address and location information, spelling mistakes, promotions and discount offers for purchasing large quantities of prescription medication, requiring payment through insecure methods such as by cryptocurrency, and insufficient product information, package content, dosing, indications, and side effects.

The evaluation and categorization of semaglutide vendor websites was conducted independently by the dissertation author and supervisor, both pharmacists, to ensure evaluation objectivity. In cases of disagreement following the initial categorization, a collaborative discussion of the individual results took place to reach a consensus. This rigorous and collaborative approach is in line with methods utilized in our previously published studies [106–109] and ensures a comprehensive and accurate assessment of online pharmacy legitimacy.

3.2. Test Purchasing

The selection process of websites for test purchasing involved assessing several variables, including the listed product formulation (either the Ozempic injection pen or a generic semaglutide injection vial), lack or requirement of a valid prescription, promotion of off-label or unauthorized use, vendor's address and location, shipping conditions and restrictions, price, payment methods, and the comprehensiveness of the product description such as information related to side effects and precautions. We aimed to document potential medication and patient safety issues originating from information provided by online vendors. For the purposes of this study, certain websites were excluded from detailed content analysis and test purchase. These exclusions include

referral sites not offering products directly for customers, duplicate content websites (different domains with identical content), ones requiring sending prescription before purchase, vendors not delivering products to Hungary or the United States, and sites offering products at exceedingly high prices. Each step of the online ordering procedure was photographed, and video recorded. These data were stored on physical hard-drives as well as backed up online on OneDrive cloud storage for future reference. To simulate a patient experience, a private email account was created for a virtual patient, a 38-year-old female. Following the recommended regimen simulating the first 2-week therapy of a new patient. Two 0.25 mg ampules/doses or an equivalent product was ordered from each domain. Preferred payment options used during test purchases included credit card and PayPal payments, or bank transfers. The date of online purchase, payment method, shipping fee, order and tracking numbers, all communication with sellers, information provided by courier services or customs' procedures, and time of delivery were documented. Since chemical and microbiological analyses were to be conducted in Hungary, this location was preferred for shipping. However, if a seller did not offer direct delivery to Hungary, parcels were ordered to California, USA, and subsequently forwarded to Hungary.

3.3. Product Assessment

3.3.1. Physical Assessment

Good Manufacturing Practice (GMP) guidelines require manufacturers to ensure that their products are appropriate for their intended use and do not place patients at risk due to insufficient safety, quality, or efficacy. This includes the packaging of pharmaceutical products, which must protect the product from physical damage, contamination, and degradation [110]. Consumers lack the resources to conduct qualitative analytical tests on the products they purchase online, consequently, visual inspection of the product's packaging at various levels -primary, secondary, and tertiary- as well as examination of accompanying documents and leaflets are often the only means of verification of product's authenticity and identifying clues signaling a product is fake, substandard or falsified.

Primary packaging is of utmost importance, as it comes in direct contact with the pharmaceutical product. It is a sealed packaging which comes in different types

depending on the dosage form. Some examples include simple glass bottles for liquids, glass or plastic injection vials, blister packs for tablets, etc. The primary packaging is designed to maintain stability of pharmaceutical products and protect them from external contaminants. Surrounding the primary packaging is the secondary packaging, typically a thin cardboard box, which contains both the primary packaging and the product information leaflet. The secondary packaging's purpose is to provide additional protection to the primary packaging and enable easier storage and transportation. The primary and secondary packaging often share certain labeling features, such as the inclusion of data matrix or QR codes, the product name, active ingredients, production and expiry dates, batch number, and manufacturer information, as well as details related to indication and usage method of the product. For medications purchased online, the tertiary packaging, which is commonly a standard padded envelope, or a cardboard box provided by the shipping company, is often the outer most layer, which simplifies product shipment and also offers an extra layer of protection for the primary and secondary packaging, ensuring the product's integrity during transit.

In order to provide a structured way of visual inspection of the product, different checklists and guidelines are available. For the purpose of this study, the International Pharmaceutical Federation (FIP) Visual Inspection Checklist [111], originally designed to assist healthcare workers in identifying substandard and counterfeit products, was adapted to evaluate the packaging and labeling of delivered products based on the methodology outlined in the published work of Schiavetti et al. [112], and our own previous research [107]. The adapted list is customized to the specific dosage form of the products and takes into account significant advances in protective measures that have been implemented since the initial publication of the FIP list, such as serialization and the implementation of data matrix or 2D codes on product packaging. The physical assessment process involved complete visual inspection and photo documentation of each delivered shipment package (tertiary packaging) and its contents, to identify the presence of visible damage or leaks, followed by inspection and documentation of the secondary and primary packaging of each product.

3.3.2. Chemical Analytical Assessment

Stock solutions of the standard and polypeptide samples were prepared in methanol. The working solutions were diluted with water/acetonitrile/formic acid (49/49/2, v/v/v). The estimated concentration of the polypeptide samples after dilution was 5 µg/mL. The final concentrations of the standard used for calibration were 5, 1, 0.5, 0.25, and 0.1 µg/mL. We used Supelco LiChrosolv LC-MS grade solvents (Merck Life Science Ltd., Hungary) for sample preparation and analysis. To prevent polypeptide adsorption and achieving high recovery, each dilution step was performed using low protein binding Eppendorf Protein LoBind microcentrifuge tubes (Eppendorf, Hamburg, Germany). The prepared calibration standards and samples were transferred to 0.5 mL low protein binding Eppendorf tubes and 5 µl of each sample was injected from a special Eppendorf carrier plate. Chromatographic separation was performed on a Thermo Ultimate 3000 UHPLC™ system (Thermo Fisher Scientific, Waltham, MA, USA) with a Luna Omega PS-C18 reversed-phase column (1.6 µm, 2.1 mm × 150 mm i.d.) from Phenomenex (Torrance, CA, USA). Two different solvents were used for the multistep gradient-based separation method. Solvent A was water/formic acid (99.9/0.1, v/v), while solvent B was acetonitrile/formic acid (99.9/0.1, v/v). The gradient program included the following steps 0.0–1.0 min, the composition was adjusted to 0% B; 1.0–8.0 min, it was increased from 0% to 50.0% B; 8.0-10.0 min, from 50.0% to 100.0% B; 10.0-18.0 min, the solvent composition was maintained at 100% B; 18.0-19.0 min, the composition decreased from 100.0% to 0% B, followed by a 6 min equilibration of the column. The flow rate was 200 µL/min. Data-dependent mass spectrometric acquisition was performed using a Bruker Maxis 4G UHR-QTOF instrument (Bruker Daltonics, Bremen, Germany). The mass spectrometer was operated in positive ion mode and the scan range was set to 300–2200 *m/z*. The flow rate of the nebulized gas was 6 L/min at a pressure of 2 bar, and the temperature was set at 180°C. The nebulizer gas composition consisted of > 99.5% nitrogen and > 0.5% other atmospheric gases. The capillary voltage was 3.8 kV, and the 10 most intense compounds were selected for CID fragmentation. All data were processed using the Data Analysis 4.4 software package. The concentration of the active ingredient in the samples was consistently high, with the parent ion intensities exceeding the instrument's detection range. As a result, the determination of the limits of quantification (LOQ) and detection (LOD) was deemed unnecessary.

3.3.3. Microbiological Assessment

Sterility and microbiological contamination testing were conducted on lyophilized peptide samples purchased from Semaspace, Biotech Peptides, and US Chem Labs to assess product quality. Testing was performed at the ISO 14644-1 certified microbiology laboratory of PharmaValid Ltd. in Budapest, Hungary. Sterility testing was performed by direct injection technique according to the guidelines of the European Pharmacopoeia (Ph. Eur. 11.0 2023 2.6.1) and the United States Pharmacopeia (USP-NF2023 ISSUE 2 <71>), and bacterial endotoxin content measurement was performed by kinetic turbidimetry technique according to the guidelines of the European Pharmacopoeia (Ph. Eur. 11.0 2023 2.6.14) and the United States Pharmacopeia (USP-NF 2023 ISSUE 2 <85>). Endosafe® KTA2TM LAL (Limulus Amebocyte Lysate) reagent and *E. coli* O55:B5 control standard endotoxin were used. Samples were stored at 20–25°C during the course of the analysis. For Semaspace and Biotech Peptides products, the contents of each vial were dissolved in 2 mL of bacteriostatic water for injection provided by each manufacturer. US Chem Labs did not include the solvent required for reconstitution; therefore endotoxin-free water was used during laboratory testing.

4. RESULTS

4.1. Online semaglutide Vendors

Following the evaluation of 1080 links from SERPs, we identified 317 links related to online pharmacies (n/N%=317/1080=29.35%). Among these, 183 links led to legitimate pharmacies (n/N%=183/317=57.73%), while 134 links directed users to 59 illegal pharmacy operations and vendor websites (n/N%=134/317=42.27%). It is worth noting that out of the 59 illegal pharmacies, 21 appeared multiple times in the SERPs, with semaspace.com being the most frequent, appearing in a total of 11 links. Semaspace.com's website displayed several typical characteristic features of illegal internet pharmacy operations, including highlighting no-prescription sales, discreet delivery, and promises of the lowest prices and money-back guarantees **(Figure 5.)**.

We discovered listings for various pharmaceutical products, including parenteral preparations like the Ozempic pen, unbranded semaglutide injection vials, and oral semaglutide tablets. The remaining SERP links were to non-sales informational websites, news, research sites, and other websites that don’t directly engage in the sale of

pharmaceutical products (n/N%=615/1080=56.94%), along with 148 links to telemedicine sites (n/N%=148/1080=13.70%).

We used the Safe Pharmacy database to assess the websites' legitimacy and found that 47.46% (n/N%=28/59) were listed as not recommended, while 52.54% were not found in the database (n/N%=31/59), which demonstrates the significant challenge NABP faces in maintaining a comprehensive and up-to-date registry of illegal online pharmacies. A review of the LegitScript.com database showed similar results, with 47.46% of the websites (n/N%=28/59) classified as "rogue", 23.73% (n/N%=14/59) as "unapproved", and 28.81% (n/N%=17/59) as "unlisted". Our results also indicated that remarkably, 18.64% (n/N%=11/59) of the illegal pharmacy domains were absent from both databases, illustrating the difficulty in maintaining a current list of illegal online pharmacies due to the ever-changing landscape and the evasive nature of these illegal operations. Demographic analysis of the domains showed that about a third of the sellers (n/N%=19/59=32.20%) didn't provide contact details or location information on their sites.

Out of the disclosed locations, Canada and the United States were most predominant, with 30.51% (n/N%=18/59) and 22.03% (n/N%=13/59) of the total, respectively. This tendency was similarly evident in the WHOIS registration data, which showed 30.51% (n/N%=18/59) of the domains were registered to entities located in the United States and 13.56% (n/N%=8/59) in Canada followed by Iceland as the third prevalent location with 8.47% (n/N%=5/59) of the domains. Registrant location information for 23.73% (n/N%=14/59) of the domains was withheld by the registrar citing privacy laws. We also examined the hosting services, finding that a considerable proportion, 76.27% (n/N%=45/59) of the illegal websites, were hosted in the United States and Canada, with Cloudflare Inc. being a preferred Canadian service provider, hosting 27.12% (n/N%=16/59) of these illegal websites.

Web traffic analysis provided by Similarweb Ltd. [113] for the period of our investigation showed that between July to September 2023, the top 30 domains accumulated over 4.7 million visits, with the top five websites attracting more than 58% (n/N%=2,730,848/4,705,502) of the total traffic. This indicates a significant concentration of visits among the top sites, while the bottom five acquired just over 1.55% (n/N%=73,166/4,705,502) of the total visits, demonstrating a significant unevenness in visitor traffic, displaying how traffic drops off as we go towards the bottom of the list.

The most visited sites included both traditional illegal pharmacies and new peptide-focused vendors, reflecting a rising interest in purchasing peptide-based products.

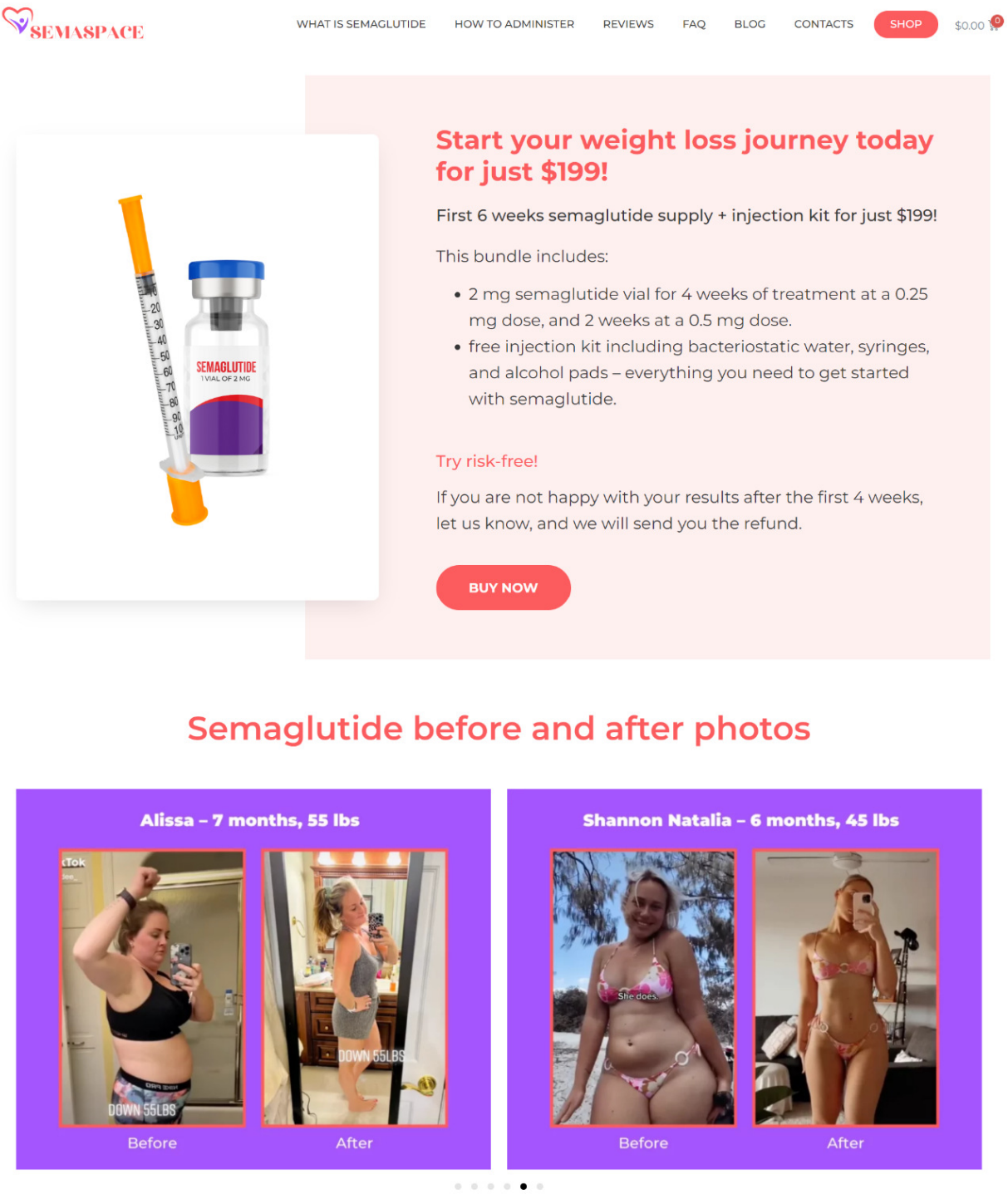

Figure 5. Screenshot of semaspace.com, the most prevalent illegal online pharmacy in our search engine results with 11 total links. Website content shows several elements of a typical illegal online pharmacy such as lack of prescription requirements, promoting off-label use of prescription drugs, best price, and money-back guarantees.

4.2. Test Purchasing and Product Delivery

Six online vendors offering parenteral semaglutide products were selected for comprehensive content evaluation and test purchases **(Table 2.)**. These six rogue domains were selected based on their high prevalence in the SERPs, offering easy access to semaglutide products without a prescription, and affordability. All six online vendors were categorized as illegitimate by the LegitScript and/or NABP verification databases. Three websites offered Ozempic injection pens for sale, while the other three sold vials of lyophilized semaglutide powder to be reconstituted prior to injection by the user. The price for the smallest available dose and quantity ranged from US$113 to US$360 (mean±SD: US$218.5±93.6). Payment options varied depending on the sellers. One domain offered only one payment option, while the rest provided various opportunities for payment, with 4 (66%) vendors offering cryptocurrency payment. None of the vendors (0%) required a medical prescription or any health-related information from patients before or during the purchase, with Ozempic pen sellers even explicitly marketing their products as available without prescription. All vendors (100%) referred to weight loss and obesity on the product page and promoted the unauthorized and off-label use of Ozempic or semaglutide containing products for weight loss. This lack of oversight was evident for both Ozempic injections and semaglutide powder sold in vials. The product descriptions of the semaglutide vials provided by peptide sellers were ambiguous, with descriptions suggesting both research and therapeutic uses. Despite some sellers labeling products “not for human use” or “research chemical” or “research use only”, descriptions often highlighted the health benefits of GLP-1 agonists for weight loss, citing scientific studies. Moreover, the same sellers proceed to send water for injection and syringes together with the product, which means warnings are likely just a calculated effort to shield themselves from legal liability, and not because these vendors actually care about patient safety. Semaspace.com, not only did not have any warning messages on the website or the product labels, but they have a dedicated before and after image gallery on their website as “success stories” (see **Figure 5.**) and went far and beyond to encourage use, by explicitly providing instructions on how to mix semaglutide with bacteriostatic water and included a dosing and injection guide, they also included 4 packs of 10 syringes and alcohol wipe prep pads in the package. The other two peptide sellers did not communicate how to reconstitute or administer the product. Overall, instructions for use, storage, and administration were provided by four out of six vendors on their website.

Domain	# links	Top-10 SER link	LegitScript Verification	NABP category	Product form and dosage	Product price* (+shipping fee)	Payment options	International shipping	Prescription requirement	Assessment of patient health status	Health related benefits	Instructions
semaspace.com	11	Yes	N/A	Not recommended	Semaglutide vial (2 mg)	199 USD / vial (+30 USD)	PayPal only	No, USA only	No	No health status required by seller	Yes, obesity	Yes
wieghtcrunchshop.com	9	Yes	Rogue	Not recommended	Ozempic pen (0.25 mg)	190 USD /1 amp (+30 USD)	Apple & Google pay/ Zelle, bank stranfer, Osko, Bitcoin	Yes	No, “without prescriotion” highlighted	No health status required by seller	Yes, weight loss	Yes
uschemlabs.com	5	Yes	Rogue	N/A	Semaglutide vial (1 mg)	148.9 USD / 5 vials (+25 USD)	Credit card, CashApp, crypto-currencies	Yes	No	No health status or professional qualification requested	Yes, weight loss, blood sugar regulation	No
biotechpeptides.com	5	Yes	Rogue	Not recommended	Semaglutide vial (3 mg)	113 USD /vial (no shipping fee)	ACH, CashApp, Venmo, Credit card	Yes**	No	No health status or professional qualification requested	Yes: appetite, cardiovascular	No
puremedsonline.com	4	No	Rogue	Not recommended	Ozempic pen (0.25 mg)	300 USD/ 2 amp. (+30 USD)	PayPal, Zelle, Bitcoin	Yes	No, “without a doctors prescription now!!!” Highlighted	No health status required by seller	Yes: diabetes, weight loss, cardiovascular	Yes
genius-pharmacy.com	4	No	Rogue	Not recommended	Ozempic pen (0.25 mg)	360 USD/ 2 amp. (+50 USD)	Bitcoin, Zelle	Yes	No “No Rx required” highlighted	No health status required by seller	Yes: weight loss, diabetes	Yes

* Smallest quantity offered for sale, ** Seller did not ship directly to Hungary.

Table 2. Summary of vendor characteristics and the description of semaglutide containing products offered by websites selected for test purchasing in August 2023.

Figure 6. Content of the shipment sent by Semaspace. A free injection kit containing bacteriostatic water, syringes and alcohol pads are included along with the semaglutide vial.

All online test purchases were completed quickly, with most online vendors offering untraceable payment methods. Payment with cryptocurrency was encouraged and incentivized by offering a 5% discount or free shipping during the checkout process. On biotecpeptides.com, customers had to acknowledge their understanding of the products' intended use for licensed researchers or professionals, explicitly stating that the products were not for human or animal use. Similar terms were found on uschemlabs.com.

All purchases were confirmed by email, only uschemlabs.com and biotechpeptides.com offered immediate credit card payment options. The remaining four sellers (66.6%) instructed customers to finalize their payments through follow up emails, with cryptocurrency being highlighted as the preferred method, vendors provided tutorials on using bitcoin with a credit card or Cash app. However, we successfully negotiated with each seller to use bank transfer or PayPal as alternative payment methods.

After the initial email communication, seller shifted to WhatsApp Messenger for further communication and providing detailed instructions on how to send the required amount

of payment (see **Figure 7.**). The process for PayPal payments was uniform across vendors: first, they sent their PayPal username via email, followed by detailed payment instructions communicated through email, their website, and WhatsApp.

These instructions specified that the payment description should only contain the customer's name and emphasized that the payment type should be marked as “For Friends and Family” to avoid order cancellation. Despite successful transactions, none of the Ozempic injections were shipped and we only received the lyophilized semaglutide product. Upon contacting the Hungarian National Customs Office for further investigation, we could confirm that illicit vendors advertising Ozempic pens are “non-delivery e-commerce scams” and do not intend to ship any products.

These scammers take advantage of the growing popularity of certain medications and shortages occurring in the legitimate supply chain to attract customers. The scam operations not only charge customers for purchases that are never delivered, but they employ a so-called “customs clearance advance-fee scam” as well, to take as much money as possible out of their victims by demanding additional fees for customs clearance. The most common method involves providing a fake tracking number that takes the victims to a fake tracking website operated by the scam networks. These fake courier websites are updated by the scammers to deceive victims into believing that their package is held up in customs and needs additional payment to be released.

We documented 3 separate scams each asking for different fees including a US$1,200 “Insurance fee”, a €450 so-called “X-ray Custom Stamps” and US$650 for “Insurance and Prescription stamps” to facilitate the clearance through Hungarian customs, with sellers promising full or partial refund of the fees upon successful delivery.

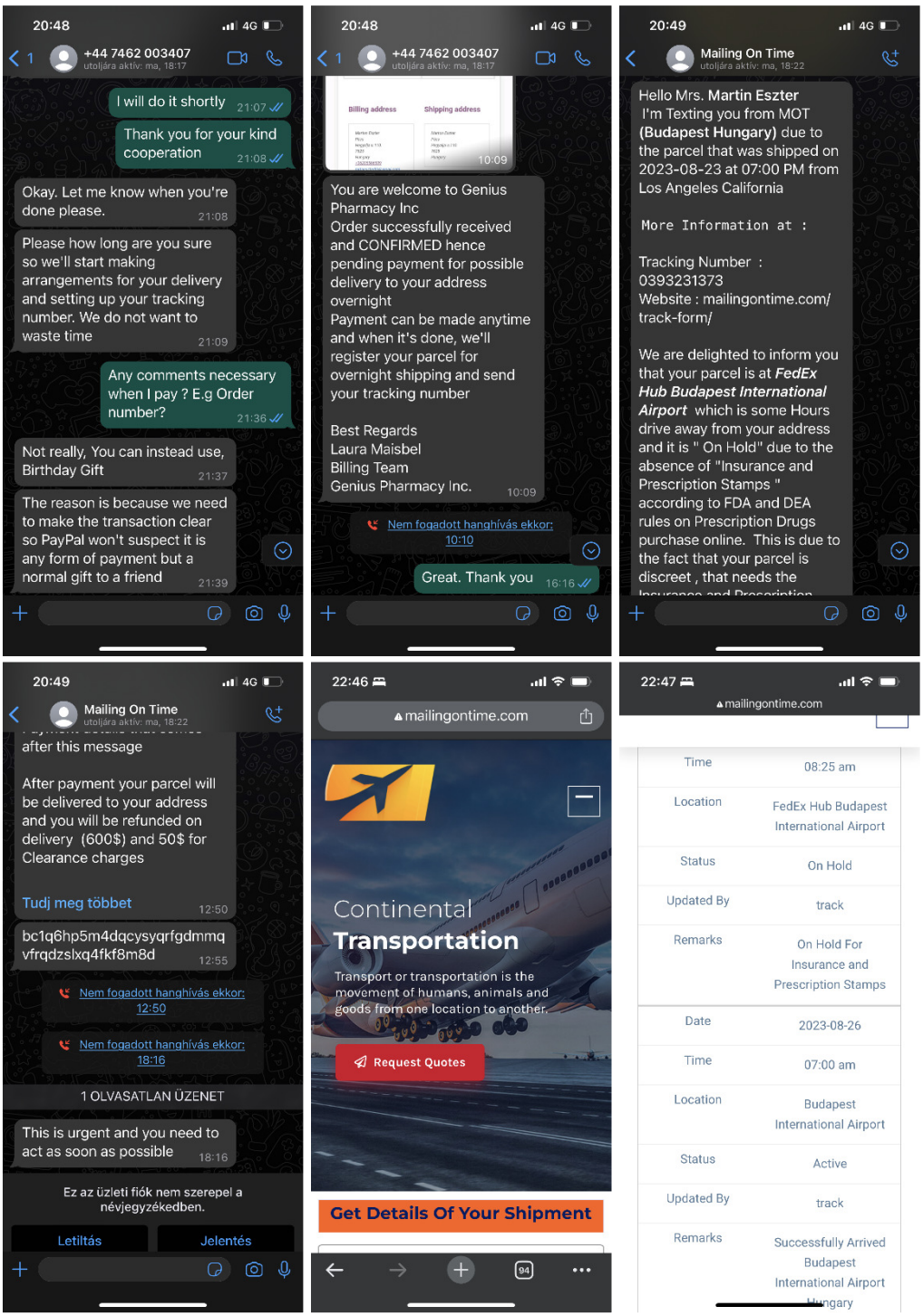

Figure 7. Series of screenshots documenting Ozempic purchase from genius-pharmacy.com, with seller communication via WhatsApp. It highlights characteristics of an e-commerce scam, including advice to disguise PayPal payments as “Birthday Gift” to avoid detection, and advance-fee scam communication with fake package tracking.

4.3. Physical Assessment of Delivered Products

We utilized an updated FIP checklist for the visual inspection of delivered products which was tailored specifically for this study by adapting a 22-item checklist for assessing the quality, safety, and regulatory compliance of the products to meet the specific needs of our project and the product's specific dosage form **(Table 3.)**. This tailored checklist includes a detailed examination of the container's integrity to prevent external contamination and ensure product stability throughout its intended shelf life. The checklist also evaluates legal requirements, such as registration with appropriate drug regulatory authorities and valid marketing authorization.

The accuracy of labeling information, including the correct spelling of active ingredients and consistency with trade names and registrations, was another focal point of the evaluation. The checklist also verifies the presence of track and trace labels, storage condition instructions, and the inclusion of detailed informative product leaflets, all vital elements of patient safety and regulatory adherence.

Figure 8. Injection vials containing lyophilized semaglutide peptide purchased from 3 illegal online pharmacies. US Chem Labs and Biotech Peptides included purity information and warnings on the vial, while Semaspace labeling lacked any such information.

In our analysis, authentic Ozempic achieved a full score of 22, indicating perfect adherence to the checklist's criteria. The illicit products managed to meet only a limited number of listed criteria, such as using a suitable container and closure for primary packaging, securely sealing the glass vial and effective protection of the product from external environment. Additionally, the active ingredient's name was present on the package, spelled correctly, and the active ingredient's amount and unit were provided on

the label. The manufacturer's name and logo were also included on the sticker labels on each glass vial. However, these preparations did not adhere to any of the remaining requirements, and as a result, lyophilized semaglutide products from semaspace.com, biotechpeptides.com, and uschemlabs.com scored significantly lower than the authentic product, only gaining 9, 8, and 8 points out of 22, respectively.

Criteria	***Genuine Ozempic***	***Semaspace***	***Biotech Peptides***	***US Chem Labs***
Does the track and trace labeling (Data Matrix, QR code or similar) look authentic?	1	0	0	0
Does the container and closure protect the product from the outside environment; e.g. is the container choice appropriate for the product?	1	1	1	1
Do they assure that the product will meet the proper specifications throughout its shelf life?	1	0	0	0
Are the container and the closure appropriate for the product inside?	1	1	1	1
Is the container safely sealed?	1	1	1	1
If there is a carton protecting the container, does the label on the carton match the label on the container?	1	1	0	0
Is all information on the label legible and indelible?	1	1	1	0
Is the medicinal product (trade name) registered in the country by the Drug Regulatory Authority)? Is the product legally sold in the country?	1	0	0	0
Is the active ingredient name spelt correctly?	1	1	1	1
Do the trade name and the active ingredient names correspond to the registered product?	1	0	0	0
Does the symbol ® follow the trade name?	1	0	0	0
Is the strength - the amount of active ingredient per unit - clearly stated on the label?	1	1	1	1
Is the dosage form clearly indicated on the container label?	1	0	0	0
Is the dosage clearly indicated on the label?	1	0	0	0
Does the dosage form stated on the label match the actual dosage form of the medication?	1	0	0	0
Is the indicated medicine under this dosage form registered and authorised for sale in the country?	1	0	0	0
Are the manufacturer's name and logo legible and correct?	1	1	1	1
Are the storage conditions indicated on the label?	1	1	0	1
Are the manufacture and expiry dates clearly indicated on the label?	1	0	1	0
Has this company or its agent registered the product in the country?	1	0	0	0
Is the manufacturer's full address legible and correct?	1	0	0	0
Does the packaging contain a leaflet explaining dosage, the medicine content, the adverse affects, the medicine’s actions, and how the medicine should be taken?	1	0	0	1
OVERALL SCORE	**22**	**9**	**8**	**8**

Table 3. Checklist for visual inspection of medicines and corresponding scores for each semaglutide product obtained from 3 illegal online pharmacies.

These low compliance scores obtained by the illegal vendors highlight serious deficiencies in a wide range of areas such as regulatory compliance, accurate labeling, and supply of essential product information, which clearly signals the inherent risks of purchasing pharmaceutical products from unauthorized online vendors.

4.4. Quantitative and Qualitative Analysis Results

4.4.1. LC-MS Analysis Results

Semaglutide polypeptide can be accurately identified and quantified using mass spectrometry, by its distinctive peak at 1029.3 Da $[M+4H]4^{+}$ in the mass spectrum, which serves as an essential reference point for accurate analytical measurements. The impurities found in peptide products synthesized using modern automatic peptide synthesizer devices vary significantly. These impurities often include unwanted synthesis by-products, solvent residues, or chemicals used for peptide chain protection. However, identification of these substances via mass spectrometry can be challenging due to their low molecular weight and ionization efficiency. Ensuring pharmaceutical product integrity requires rigorous monitoring of the manufacturing process. This includes oversight of the active pharmaceutical ingredient, impurities, and potential contaminants that might result from cross-contamination during production. In our study, we evaluated the purity and quantity of active ingredients in the samples, which were tested for polypeptide impurities. The chromatographic analysis showed one primary signal for semaglutide in each sample, suggesting the absence of peptide-like impurities.

We identified significant discrepancies between the purity levels claimed by vendors (at least 99%) and the actual semaglutide content of the delivered product as determined by our LC-MS analysis. Products from Semaspace, US Chem labs, and Biotech Peptides showed significantly low polypeptide concentrations of 14.37%, 8.97%, and 7.70%, respectively, indicating much lower purity. This discrepancy suggests the presence of low-mass, poorly ionizing impurities, necessitating further investigation with additional analytical methods to identify these contaminants definitively. These impurities likely reflect inadequate or skipped purification steps in the manufacturing process, which are crucial but also time-consuming and expensive [114,115].

By measuring the content of each vial, we determined the actual amount of API in each sample. It is important to note that none of the products contained the accurate amount of semaglutide as stated. In fact, all three products had significantly higher API levels than what was declared on their labels. Specifically, products from Semaspace and US Chem labs contained an astonishing 39% and 34% more semaglutide than indicated respectively, whereas the product from Biotech Peptides had a 29% higher concentration of semaglutide than what was advertised.

Sample	Total Weight of Powder in Vial	semaglutide Content indicated on Label	Measured semaglutide Content	Labeling Accuracy	Purity Indicated on Label or Website	Measured Purity
Ozempic 1 mg solution for injection in pre-filled pen* (reference)	N/A	1 mg	1.05±0.02 mg	105.05%	N/A	N/A
Biotech Peptides powder, vial	50.1 mg	3 mg	3.86±0.14 mg	under-labeled (129%)	99%	7.70±0.28%
Semaspace powder, vial	19.3 mg	2 mg	2.77±0.12 mg	under-labeled (139%)	99%	14.37±0.63%
US Chem Labs powder, vial	14.9 mg	1 mg	1.34±0.07 mg	under-labeled (134%)	99%	8.97±0.51%

*Based on the official Ozempic European public assessment report (EPAR) product information document published by the European Medicines Agency [116], one pre-filled Ozempic 1 mg pen contains 4 mg semaglutide in 3 ml solution. Pen is designed to deliver 4 doses of 1 mg (0.74 ml/dose).

Table 4. Results analytical measurements for each semaglutide product obtained from 3 illegal online pharmacies and original Ozempic reference product.

These findings highlight substandard manufacturing practices by these rogue vendors, highlighting the risks associated with obtaining pharmaceutical products from these illegal sources.

4.4.2. Microbiological Testing Results

We utilized the endotoxin kinetic turbidimetry assay, which has a detection limit of <0.01 EU/ml, to evaluate the bacterial endotoxin content of samples. After adjusting for sample dilution and measuring changes in turbidity over time, we found endotoxin levels to be <2.8658 EU/mg for product from US Chem Labs and <2.1645 EU/mg for Biotech Peptides. However, in the case of the sample from Semaspace we identified a

higher endotoxin level, measured at 8.9511 EU/mg. Presence of endotoxin indicates contamination by Gram-negative bacterial cell wall components. As two of the packages were delivered along with a standard commercial bacteriostatic water for injection, a commercial product not produced by the illegal vendors, we could assume that the contamination likely arises from either the water or non-sterile components used by vendors during the lyophilized peptide production process. Identifying the precise source of the endotoxin, however, is not feasible without access to more information and production facilities. Sterility testing was also performed on all products and confirmed that all three lyophilized peptide samples were free from viable microorganisms, indicating that they were sterile at the time of examination.

5. DISCUSSION

The rapid expansion of the online pharmaceutical market, underscored by the convenience and accessibility of internet pharmacies, has significantly influenced consumer behavior worldwide. A survey of 1055 individuals conducted by Fittler et al. in 2018 revealed that 4.17% of participants had purchased medications and 18.4% had bought other healthcare and supplements online [117]. A follow up online survey by the same researchers in 2022 showed a substantial rise in the online purchases, with 55.48% of the responders stating they had purchased medication online and 63.0% had purchased health products online following the COVID-19 pandemic, indicating that the coronavirus pandemic has further encouraged the trend of online medication purchasing [12]. This transformation has not only facilitated access to online sources of medications and health products for a larger segment of the population but also introduced challenges such as the proliferation of illegal online pharmacies and increased the exposure to risks associated with counterfeit drugs.

According to a recent analysis of the landscape of informal and illegal markets of substandard and falsified medical products published by WHO [118], online illegal markets have gained a foothold in middle-income countries, primarily focused on selling antibiotics, antihypertensives, abortion pills and medicines for erectile dysfunction. In contrast to the situation in low and middle-income countries, illicit vendors targeting high-income countries are involved in distribution of a broader spectrum of medical commodities in addition to the sales of counterfeit medications, such as intrauterine

contraceptive devices, essential medical supplies and personal protective gear, COVID-19 tests, and even ventilators [118]. The worldwide illicit medicine trade extents from production centers in India and Pakistan, China, Hong Kong, Russia and Latin America to major distribution networks across the Middle East, Africa and Central Europe, which follows typical supply chain patterns [119,120]. Europe's legal pharmaceutical supply is largely secure due to regulatory controls, and substandard or falsified medicines primarily flow through these concealed global channels with limited infiltration into the legitimate European supply chain [120–122].

With the online pharmacy market projected to reach US$81.37 billion by 2028 [16], and the staggering estimation that 96% of the total online pharmacies were operating illegally and failing to adhere to legal and safety requirements [33], the implications for patient safety, public health, and the integrity of the online pharmaceutical supply chain are profound.

Our study's primary focus was on investigating and documenting the illegal online trade of Ozempic and semaglutide, which is a newly authorized GLP-1 receptor agonist originally intended for management of diabetes, which later became popularized for weight loss. Semaglutide represents a modern approach to diabetes management and weight loss pharmacotherapy, offering up to a 15% reduction in body weight and improvements in glycemic control and cardiovascular risk factors [79]. Due to celebrity endorsements and extensive news coverage, semaglutide is now widely used off-label by individuals for cosmetic weight-loss, which has resulted in worldwide shortages, limiting access to patients that rely on this medication for treatment of diabetes.

The Ozempic craze shares some striking parallels with the previously much-publicized illicit trade and counterfeiting issues surrounding Viagra. Both drugs have experienced a surge in demand and illicit trade fueled by their perceived benefits and efficacy, coupled with high regard attached to them in popular culture. However, the current Ozempic trend is progressing in a distinctly different media and technological landscape compared to the Viagra's peak in the early 2000s. The Ozempic black market leverages social media, modern telecommunications and e-commerce platforms, which shapes the long-term impacts on public health and policy in distinct ways, when compared to previous experiences with popular illegally traded medications such as Viagra.

Our study's findings indicate a significant presence of illegal online pharmacies trading semaglutide containing products, with close to half (42.27%) of the total identified online pharmacy links leading to 59 illegal operations. This proliferation of illicit semaglutide vendors is a direct consequence of supply-demand mismatches and highlights the critical need for stringent surveillance and regulatory enforcement to protect consumers and maintain the integrity of the pharmaceutical supply chain.

Our investigation revealed a concerning number of visitors rushing to these identified illegal vendors, and possibly purchasing counterfeit products, which pose significant risks for consumers seeking to purchase Ozempic or semaglutide online, due to the unverified quality and unknown safety profile of these products. The frequent appearance of certain illegal vendors in search engine results, particularly semaspace.com, demonstrates active use of illegal SEO techniques by these vendors to reach high search engine ranking and maintain visibility and accessibility to potential customers.

Our investigation and identified illegal vendors are in line with recent announcements by the FDA, which has issued warning letters [123,124] to Semaspace and US Chem Labs, two of the illegal vendors we investigated and performed test purchases from in our study.

Although for the purpose of this study we only evaluated online pharmacy websites accessible through SERP links, it is important to note that the consumers looking for purchasing medications on the internet are not limited to online pharmacies, and they have a wide range of sources to choose from, such as purchasing medications directly through online interaction with users on popular social media platforms. A wide range of substances were reported as being sold through social media including not only common recreational drugs such as marijuana, LSD, and ecstasy/MDMA, but also prescription drugs such as stimulants, opioids, and benzodiazepines [4,125]. Popularity of social media applications among illegal drug sellers is attributed to their efficiency in bridging the gap between buyers and sellers, as they offer a more convenient and secure direct communication, even allowing for the previewing of products using photo and video [126].

As a result, dealing on social media has become a more attractive alternative to traditional street dealing or setting up an online pharmacy website for small scale illegal operations. We identified several large online forums specialized in providing advice on weight loss using semaglutide and off-label Ozempic, with some forums even operating peer-to-peer markets allowing sales between members and so called "trusted sellers". Investigation of

illegal sales of semaglutide on these forums and on different social media platforms was not in the scope of this study but could be an opportunity for future research.

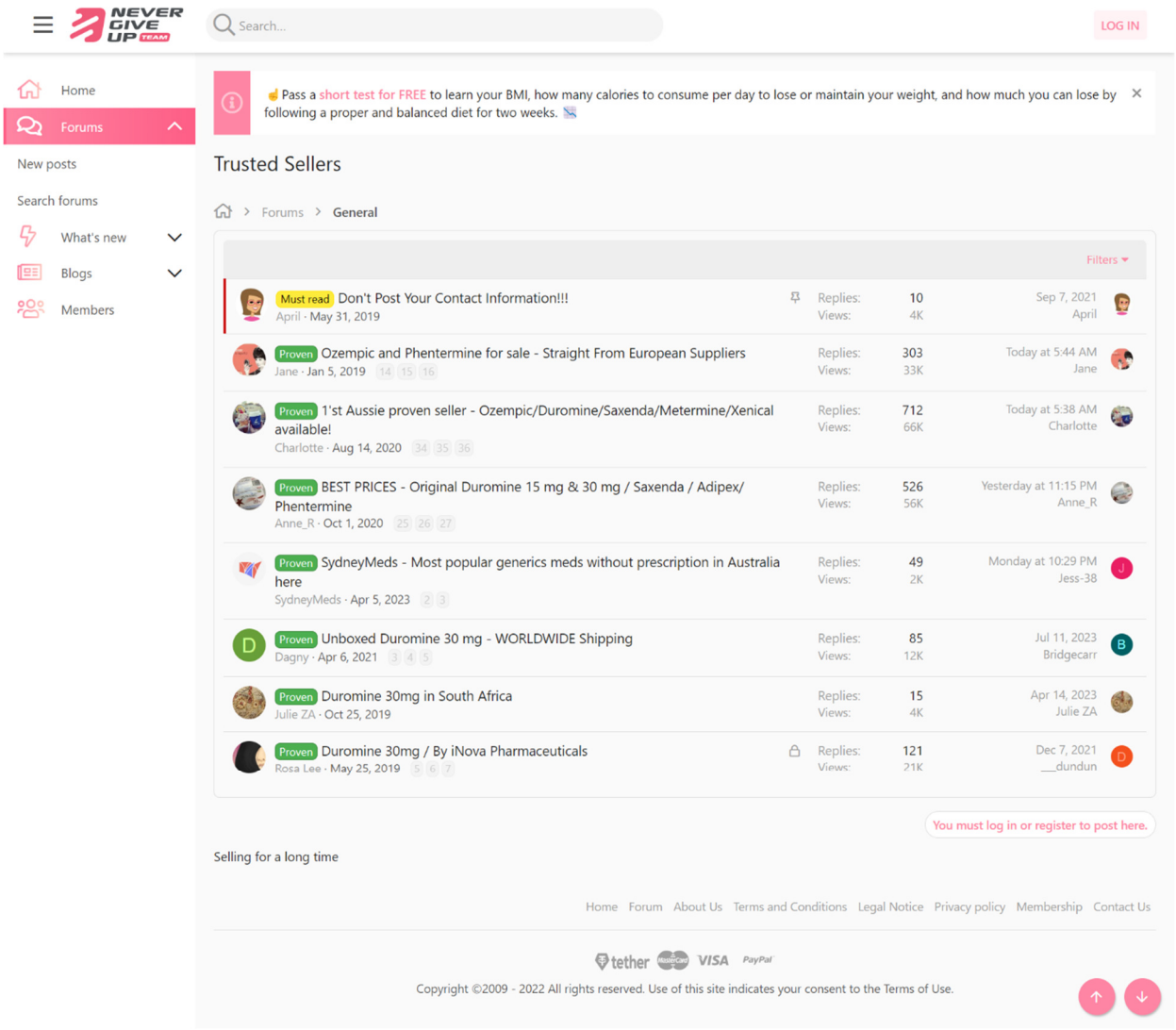

Figure 9. Screenshot of a popular weight loss forum. These online communities often provide marketplace subforums that is used by illegal vendors for direct sale of the counterfeit products. These forums often require registration and logging in to view posts and interact, which makes them harder to investigate by authorities, thus can operate unchallenged for a long time before they are shut down.

During our research on the prevalence of illegal online pharmacy links in recommendations offered to users by new generative AI-integrated search engine platforms, we identified inadvertent direct promotion of illegal online pharmacy websites in the replies generated by the AI in response to user questions related to purchasing medications online [127]. This new vulnerability may be linked to the rogue SEO

techniques used by illegal online pharmacies to gain high rankings on SERPs, that is now helping them influence generative AI's response and find their way into the recommendations in the new search engine chat interfaces.

An example of this new vulnerability is demonstrated in **Figure 10.**, which shows the AI response generated by Bing Chat for *"buy Ozempic online"* includes a mixture of legal (pharmacylanet.com, goodrx.com and amazon.com) and illegal internet pharmacies (puremms.com and buyozempic.com) in the embedded links, along with links to other informational websites (such as Ozempic.com which belongs to Novo Nordisk).

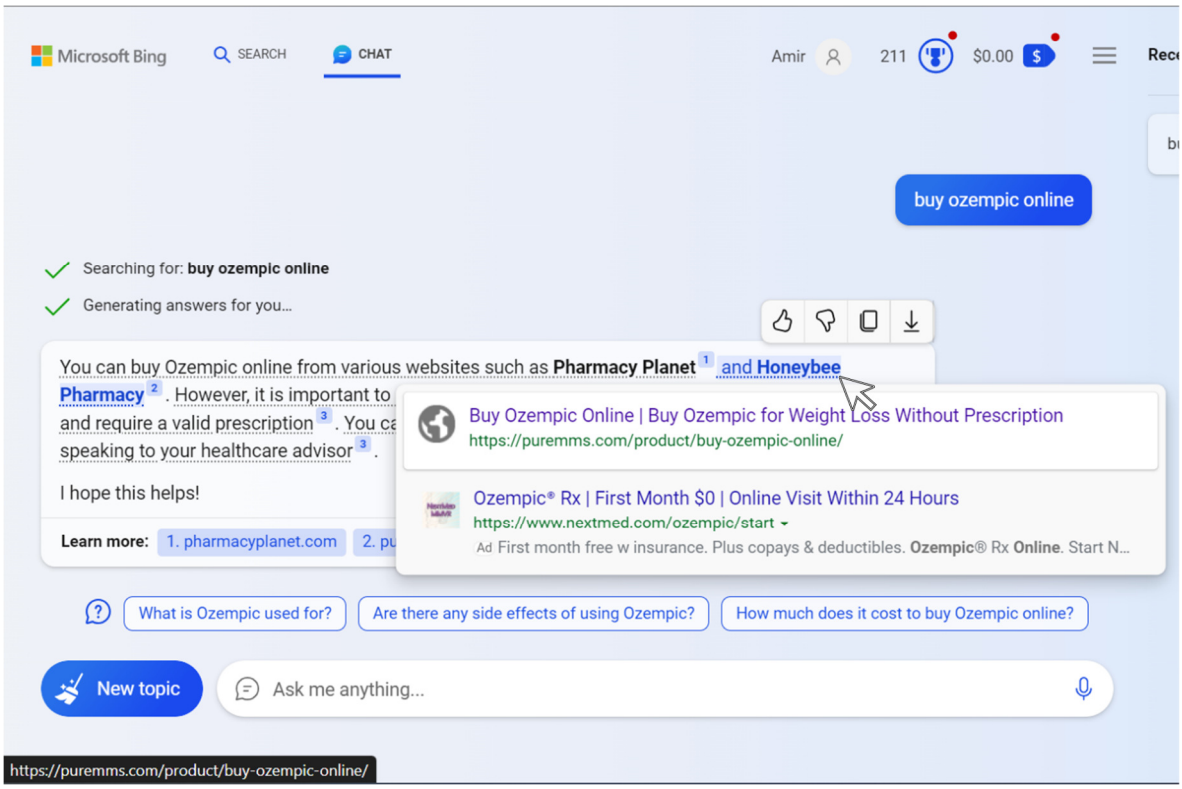

Figure 10. Screenshot of Bing Chat's response to "buy Ozempic online" with a mixture of legal (such as PharmacyPlanet and Amazon) and illegal (such as PureMMS.com and BuyOzempic.com) internet pharmacies recommended.

Although the total count of illegal pharmacies was not overwhelmingly high in AI-generated recommendations, their mere presence is a significant potential public safety risk which signals the need for introduction of appropriate countermeasures.

Our demographic analysis of identified illegal vendors revealed a large number of illegal websites hosted in the United States and Canada, with Cloudflare Inc. as a preferred

service provider. These discoveries point to the need for closer scrutiny of hosting services that may inadvertently facilitate the operation of illegal pharmacies. The test purchasing component of our study highlights the ease with which consumers can access semaglutide products without a prescription, with none of the vendors requiring medical information from buyers. The promotion of unauthorized and off-label use of semaglutide for weight loss on these platforms is particularly concerning, as it suggests a disregard for patient safety and regulatory guidelines.

Our study has uncovered two main fraud strategies used by illicit vendors specifically targeting medications with high global demand and affected by shortages. The first strategy involves e-commerce fraud, where online criminals create fake pharmacy websites offering unrestricted access to prescription-only medications that, in reality, are never shipped. A second strategy involves financial exploitation with advance-fee scams, which is achieved through referrals to fictitious third-party courier services demanding additional customs fees. These fraudulent practices not only result in financial loss for the consumer but can also pose a significant public health risk by potentially delaying or preventing access to legitimate medical treatment for chronic patients that are tricked into purchasing their regular medication from these websites.

The physical, chemical, and microbiological assessments conducted on semaglutide products obtained through test purchasing from illegal pharmacies provide critical data on the quality and safety of these preparations. Physical assessment of delivered products revealed multiple serious deficiencies compared to the authentic Ozempic product, for instance inappropriate product packaging, inaccurate labeling, and the lack of essential product information leaflets, which resulted in low scores on the adapted FIP checklist for these products. Microbiological testing revealed the presence of bacterial endotoxins in the samples, with one sample from Semaspace showing notably higher levels than the products from other two vendors, suggesting possible contamination during the production process. However, despite the presence of endotoxins, sterility testing confirmed that all samples were free from viable microorganisms at the time of examination, indicating sterility. The LC-MS analysis results demonstrated a significant discrepancy between the purity levels claimed by vendors and the actual semaglutide content of the delivered products. We identified a stark contrast between the claimed purity levels of at least 99% and significantly lower actual semaglutide content of between 14.37% and 7.70% which suggests the presence of low-mass, poorly ionizing

impurities, indicating inadequate and substandard production and purification processes used by the illegal vendors. Furthermore, the actual amount of active ingredient in each sample was found to be higher than stated, with products containing close to 40% more semaglutide than indicated on the product label. In conclusion, our extensive evaluation and findings underscore the risks associated with purchasing Ozempic, semaglutide or any other pharmaceutical products from illegal sources, as they could potentially expose users to health hazards such as contamination and incorrect dosing.

6. Limitations

Although our study aimed to provide a complete and extensive evaluation of the illegal trade of semaglutide on the internet, we had to limit scope of our work to SERPs in order to maintain a focused approach, that was in-line with our previous research. This could result in potentially overlooking a broader spectrum of illegal vendors operating via social media, forums, and other more clandestine platforms not indexed by conventional search engines. We also chose to focus on the so called “surface web” and not include “dark web” markets for the same reasons. The test purchases were performed with a limited number of vendors and products, due to funding restrictions, as purchase of illegal products cannot be financed using institutional funding and had to be financed using personal funds. We also uncovered several scam operations which didn’t deliver any products after purchase was completed and had to test with 3 samples only out of the originally purchased 6. As a result, the samples we ultimately obtained cannot fully represent the variety of counterfeit products consumers encounter on the illicit market. We strived to perform a comprehensive laboratory analysis on the products, however testing for all possible contaminants and the impurity content in the samples would require larger quantities of products, and extensive laboratory resources, chemical standards and reagents, which were beyond the scope and resources available for this study. We acknowledge this limitation and may explore this in our future research to enhance our understanding of the impurity profiles of these products.

7. CONCLUSIONS

7.1. Key Findings and Their Implications

Key Findings:

1. **Online semaglutide vendors:** Our study identified 317 links to online pharmacies from 1080 SERP links, with 183 being legitimate (57.73%) and 134 (42.27%) leading to 59 illegal operations. Semaspace.com was highlighted as the most frequent illegal vendor.
2. **Verification challenges:** Using Safe Pharmacy and LegitScript.com databases, close to half (47.46%) of the online vendor identified through SERPs were listed as "not recommended" or "rogue", however a notable 18.64% of vendors were not listed in either database, underlining the challenge of tracking and verification of online pharmacies using existing databases.
3. **Demographic distribution:** A substantial number of illegal pharmacy operations were registered to entities based in the United States (30.51%) and Canada (13.56%), with a significant portion of the domains' registrant information (23.73%) withheld due to privacy laws, which helps illegal sellers conceal information on their inner workings. Analysis of hosting service providers showed majority of illegal websites (76.27%) were hosted in the United States and Canada, with Canadian service provider Cloudflare Inc. hosting 27.12% of the illegal websites.
4. **Web traffic analysis:** The top 30 illegal pharmacy domains attracted over 4.7 million combined total visits between July and September 2023, emphasizing the popularity of top illegal pharmacy websites.
5. **Test purchasing and product delivery:** Test purchases from six rogue pharmacies revealed several alarming issues. These illegal sellers do not require prescriptions, and they promote the off-label use of these medications. We also uncovered a serious new concerning trend of exploiting the high demand and global shortages that also affect illegal sellers of Ozempic pens, therefore they have turned to non-delivery and advance-fee scams.
6. **Physical, Chemical, and Microbiological assessments:** The physical assessment using an FIP checklist showed that illicit vendor's products failed to meet most GMP criteria, while LC-MS analysis revealed illicit products have significantly low polypeptide purity and major discrepancies between claimed and actual API

content where observed, with some samples having close to 40% more semaglutide concentration than indicated on the label, raising quality and safety concerns.

Implications:

1. **Consumer safety:** The high presence of illegal pharmacies and the sale of substandard products endanger consumer safety, especially for those using semaglutide off-label for weight loss.
2. **Regulatory oversight:** The findings stress the need for enhanced regulatory strategies to monitor and mitigate the presence of illegal online pharmacies and improve the accuracy of verification databases.
3. **Country specific enforcement:** The data on the geographic distribution of illegal pharmacies suggest a need for more robust, focused law enforcement interventions in highly affected regions like the United States and Canada, to put pressure on domain registrar's and hosting providers to shut down illicit online pharmacy operations and require better monitoring policies to prevent abuse of these services.
4. **Awareness and education:** The popularity of illegal sites and the prevalence of scams highlight the importance of educating consumers not only related to health consequences of counterfeit products but also about the financial risks associated with purchasing pharmaceutical products from unverified online sources.
5. **New vulnerabilities:** Inadvertent direct promotion of illegal online pharmacy websites in the responses generated by the new generative AI integrated search engines is a significant new potential public safety risk which highlights importance of more strict oversight as well as cooperation with search engine providers to prevent future occurrence.
6. **Opportunistic fraudulent practices:** Criminal operations running advance-fee and non-delivery scams are taking advantage of the high demand and shortages to commit e-commerce fraud, which is a complex challenge to mitigate, requiring consumer education as well as coordinated law enforcement actions.

7.2. Strategic Recommendations for Stakeholders

Our investigation has revealed a serious emerging phenomenon: simultaneous appearance of links to both legitimate and illicit online pharmacies in generative AI outputs that appear in response to user communication with the search engine chat bots

and asking for advice on purchasing medications online. These findings reinforce the critical importance of more effective and comprehensive regulatory oversight. With appropriate integration of generative AI, it is possible for search engines to systematically highlight links to certified, legal pharmacies in their responses, eliminating the persistent problem of illegal online pharmacies appearing in search results which has remained an unreserved issue for more than two decades. Improving the accuracy of generative AI in search results could significantly improve patient safety by delivering reliable information and guiding users in the direction of legitimate, safe online vendors for purchasing medicines. However, accomplishing this goal depends largely on the policy choices made by stakeholders in the design and deployment of AI-enabled technologies. With careful planning and strong regulation, the benefits of AI can be used to ensure the safety of the online pharmaceutical market and protect public health.

7.3. Directions for Future Research

To build on the findings of the current study, future research should focus on several critical areas. There's a need to examine the role of new and emerging digital platforms. As our study has demonstrated significant web traffic going to illegal pharmacy websites, it is important to examine the role of unethical and illegal SEO, and how search engine providers can combat these practices. The relationship between social media and illegal pharmaceutical product distribution needs further investigation. As social media platforms become increasingly popular marketplaces, it is critical to understand how they are used to promote and sell not only popular drugs like semaglutide, but also other new or trending drugs. This includes examining the strategies sellers use to engage with consumers and the potential risks associated with these interactions.

Our findings highlighted concerns about AI-powered search engines potentially directing users to illegal online pharmacies. Future studies should aim to identify the mechanisms by which AI algorithms could be manipulated or misled by illicit sellers and propose solutions to improve the reliability and safety of AI recommendations. Finally, ongoing research should monitor consumer demand to identify the emergence of new trending medications and persisting drug shortages to assess how quickly they are adopted and targeted by illegal online sellers. This could help regulators and healthcare professionals anticipate and respond to emerging threats in the online pharmacy landscape in order to limit risks to consumers and protect public health.

8. Acknowledgements

I am truly grateful for the unconditional love and support I received from my family and friends throughout the challenging years of my studies. Their support provided me with the strength to persevere; their patience, understanding, and willingness to make sacrifices while I was occupied with research and writing have been invaluable.

My father's words have always resonated with me during moments of doubt. He would tell the story of Thomas Edison's failed experiments with the incandescent lamp until he finally made it. After each failure Edison would say: “I have not failed. I've just found 10,000 ways that won't work.” This reminder of persistence in pursuit of solutions has been like a guiding light in my academic journey.

I would like to express my appreciation to my colleagues at the Department of Pharmaceutics, and extend my sincere gratitude to my supervisor, Dr. András Fittler, for his guidance and mentorship at every step of this journey. His openness to exploring even the oddest ideas —like trying to see if we can find illegal Ozempic online and then helping to test-purchase and analyze samples— has led to one of the most fascinating and challenging projects we have done. This project not only shaped the basis of my dissertation but also deeply influenced my academic growth.

Now that this journey comes to an end, I am reminded of another quote by Edison:

“I never did a day's work in my life. It was all fun.”
Thomas Alva Edison

9. List of Publications and Presentations

- Original research papers: 4 (Cumulative impact factor: 28)
- Conference presentations: 11

Publications directly linked to the thesis topic: (Impact Factor: 15.9)

Ashraf, AR, Mackey, TK, Fittler, A. **(2024)** Search Engines and Generative Artificial Intelligence Integration: Public Health Risks and Recommendations to Safeguard Consumers Online. JMIR Public Health and Surveillance 2024;10:e53086. https://doi.org/10.2196/53086. **(Impact factor: 8.5)**

Fittler, A., Paczolai, P., **Ashraf, A.**, Pourhashemi, A., & Iványi, P. **(2022)**. Prevalence of poisoned Google search results of erectile dysfunction medications redirecting to illegal internet pharmacies. JOURNAL OF MEDICAL INTERNET RESEARCH, 24(11). http://doi.org/10.2196/38957 **(Impact factor: 7.4)**

Presentations directly linked to the thesis topic:

Ashraf, A. R., & András, F. **(2023)**. Evaluating Online Pharmacy Market participants in Germany: Analyzing Legal and Illegal Vendors with a brief comparison to their Hungarian counterparts. In 2023 European Association of Faculties of Pharmacy Conference: Book of Abstracts ISBN:978-84-09-51373-4 (pp. 144–144).

Sebők, L., **Ashraf, A. R**., & Fittler, A. **(2023)**. Prevalence and legitimacy of online pharmacy market participants accessed via search engine query results in Hungary and Sweden. In MedPECS - Medical Conference for PhD Students and Experts of Clinical Science (pp. 58–58).

Ashraf, A. R., Sebők, L., & Fittler, A. **(2023)**. Evaluating the Legitimacy of Online Pharmacy Market Participants: A Comparative Analysis of European Countries with Different Legislative Backgrounds. In Szentágothai János Szakkollégiumi Konferencia.

Other Publications: (Impact Factor: 12.1)

Ashraf AR, Somogyi-Végh A, Merczel S, Gyimesi N, Fittler A. **(2024)**. Leveraging code-free deep learning for pill recognition in clinical settings: A multicenter, real-world study of performance across multiple platforms. Artificial Intelligence in Medicine 2024;150:102844. https://doi.org/10.1016/j.artmed.2024.102844. **(Impact factor: 7.5)**

Csikós, E., Csekő, K., **Ashraf, A. R.**, Kemény, Á., Kereskai, L., Kocsis, B., Horváth, G. **(2020)**. Effects of *Thymus vulgaris* L., *Cinnamomum verum* J.Presl and *Cymbopogon*

nardus (L.) Rendle Essential Oils in the Endotoxin-induced Acute Airway Inflammation Mouse Model. MOLECULES, 25(15). http://doi.org/10.3390/molecules25153553 **(Impact factor: 4.6)**

Other Presentations:

Ashraf, A. R., Somogyi-Végh, A., Merczel, S., Gyimesi, N., & Fittler, A. **(2023)**. Mesterséges intelligencia alapú modell fejlesztése és értékelése klinikai környezetben történő gyógyszerfelismeréshez: Három hazai kórházban végzett tesztelés eredményei. ACTA PHARMACEUTICA HUNGARICA, 93(Suppl. I.), S33–S33.

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Original Paper

Search Engines and Generative Artificial Intelligence Integration: Public Health Risks and Recommendations to Safeguard Consumers Online

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Abstract

Background: The online pharmacy market is growing, with legitimate online pharmacies offering advantages such as convenience and accessibility. However, this increased demand has attracted malicious actors into this space, leading to the proliferation of illegal vendors that use deceptive techniques to rank higher in search results and pose serious public health risks by dispensing substandard or falsified medicines. Search engine providers have started integrating generative artificial intelligence (AI) into search engine interfaces, which could revolutionize search by delivering more personalized results through a user-friendly experience. However, improper integration of these new technologies carries potential risks and could further exacerbate the risks posed by illicit online pharmacies by inadvertently directing users to illegal vendors.

Objective: The role of generative AI integration in reshaping search engine results, particularly related to online pharmacies, has not yet been studied. Our objective was to identify, determine the prevalence of, and characterize illegal online pharmacy recommendations within the AI-generated search results and recommendations.

Methods: We conducted a comparative assessment of AI-generated recommendations from Google's Search Generative Experience (SGE) and Microsoft Bing's Chat, focusing on popular and well-known medicines representing multiple therapeutic categories including controlled substances. Websites were individually examined to determine legitimacy, and known illegal vendors were identified by cross-referencing with the National Association of Boards of Pharmacy and LegitScript databases.

Results: Of the 262 websites recommended in the AI-generated search results, 47.33% (124/262) belonged to active online pharmacies, with 31.29% (82/262) leading to legitimate ones. However, 19.04% (24/126) of Bing Chat's and 13.23% (18/136) of Google SGE's recommendations directed users to illegal vendors, including for controlled substances. The proportion of illegal pharmacies varied by drug and search engine. A significant difference was observed in the distribution of illegal websites between search engines. The prevalence of links leading to illegal online pharmacies selling prescription medications was significantly higher (P=.001) in Bing Chat (21/86, 24%) compared to Google SGE (6/92, 6%). Regarding the suggestions for controlled substances, suggestions generated by Google led to a significantly higher number of rogue sellers (12/44, 27%; P=.02) compared to Bing (3/40, 7%).

Conclusions: While the integration of generative AI into search engines offers promising potential, it also poses significant risks. This is the first study to shed light on the vulnerabilities within these platforms while highlighting the potential public health implications associated with their inadvertent promotion of illegal pharmacies. We found a concerning proportion of AI-generated recommendations that led to illegal online pharmacies, which could not only potentially increase their traffic but also further

exacerbate existing public health risks. Rigorous oversight and proper safeguards are urgently needed in generative search to mitigate consumer risks, making sure to actively guide users to verified pharmacies and prioritize legitimate sources while excluding illegal vendors from recommendations.

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KEYWORDS

generative artificial intelligence; artificial intelligence; comparative assessment; search engines; online pharmacies; patient safety; generative; safety; search engine; search; searches; searching; website; websites; Google; Bing; retrieval; information seeking; illegal; pharmacy; pharmacies; risk; risks; consumer; consumers; customer; customers; recommendation; recommendations; vendor; vendors; substance use; substance abuse; controlled substances; controlled substance; drug; drugs; pharmaceutic; pharmaceutics; pharmaceuticals; pharmaceutical; medication; medications

Introduction

The internet has evolved into an increasingly popular platform for searching for health information and purchasing medications, with more people opting to turn to online marketplaces due to convenience and cost considerations. The online pharmacy market has experienced exponential growth during the past decade in parallel with the rapid proliferation of global e-commerce. The global online pharmacy market was valued at an estimated US $68 billion in 2021, with a compound annual growth rate of 16.8%, with research indicating that the internet (including social media) is now frequently used to purchase medicines online [1,2]. Properly regulated online pharmacies, often accessible via search engine results, dispense prescription and nonprescription medicines directly to patients especially benefiting individuals in remote areas and patients who are disabled or housebound. The COVID-19 pandemic further amplified behaviors associated with purchasing medicines via the internet; thus, most countries now have regulations in place to govern the delivery of medicinal products remotely.

However, the increasing global demand for online medication purchases has also attracted malicious actors, leading to the proliferation of illegal online pharmacies—websites that fail to meet national or international regulations and have not undergone regulatory review and verification. Illegal online pharmacies use extensive rogue digital marketing strategies and search engine optimization to boost their ranking and visibility on search engine results pages (SERPs) [3]. Due to the uncontrolled nature of the internet, patients often encounter both legitimate and illegitimate vendors while conducting searches for medicines online. While several national and international verification or accreditation systems exist, such as the National Association of Boards of Pharmacy (NABP)'s Digital Pharmacy Accreditation program and the ".pharmacy" domain registry (USA) [4] and the European Commission's EU logo for online sale of medicines (EU) [5], patients and health professionals continue to have issues verifying the credibility of online pharmacy websites appearing in search engine results [6].

Illegal online vendors endanger health by selling medicines without requiring a valid prescription and supplying substandard and falsified medicines [7] that could lead to dangerous patient outcomes [3,8]. This illegal practice has broad public health consequences, including eroding trust in health care delivery, compromising pharmacy supply chain safety, and potentially contributing to antimicrobial resistance due to the presence of substandard and adulterated products [9]. Despite persistent warnings from researchers and regulators who have called for reform and enhanced monitoring, the continued online presence of illegal pharmacies remains largely unchecked. Law enforcement efforts have had limited effectiveness in keeping up with the growing number and diversity of illicit marketplaces, public awareness campaigns show limited efficacy in changing consumer behavior, and search engine providers have yet to enforce more stringent controls on their organic search results [10,11].

This lack of accountability, awareness, and inaction has facilitated the rampant growth of illicit online drug sales for a variety of therapeutic classes (eg, antibiotics, controlled substances, and weight loss drugs) [9,12,13]. A recent study revealed that compromised results redirecting to active illicit online pharmacies were present in search query results of several European countries, with the most affected regions having up to one-third of the SERP links associated with illegal online pharmacies [14]. Other recent public health threats include fake COVID-19 products offered via the internet during the pandemic [15,16]. Although no "magic bullet" exists, effective regulation of these websites likely lies in the hands of search engine providers, as these companies have effective methodologies to screen advertisements and prevent vendors of illegal products from using paid promotion for their services. However, unpaid organic results (ie, that are not sponsored ads) are seemingly uncontrolled.

Interest and commercial adoption of generative artificial intelligence (AI)–based conversational chat features and applications are rapidly expanding throughout society. Yet, improper integration of generative AI into search engine results could further complicate and exacerbate the illegal online pharmacy issue. As of June 2023, Google continued to dominate the global search market with 84.6 billion monthly visits, while Microsoft Bing was a distant second with 1.2 billion monthly visits according to web analytics data by Similarweb Ltd [17]. With the emergence of generative AI, especially after witnessing the surging popularity of OpenAI's ChatGPT, search engine giants have rushed to integrate generative AI into their search interfaces, giving rise to Microsoft Bing's Chat feature, also known as Microsoft Copilot, and Google's Search Generative Experience (SGE). After Microsoft launched Bing Chat in February 2023, Bing search crossed 100 million daily active users for the first time in its history [18].

These recent developments will transform the way global users search for and interact with health information online. Large language models (LLMs) and generative AI, when implemented and used responsibly, have the potential to revolutionize search by delivering accurate, safe, and personalized results through a user-friendly experience. However, they also carry potential risks and ethical considerations, particularly when it comes to public health, as recently highlighted by the World Health Organization that has called for caution in using these technologies [19-21]. LLMs, lacking the ability to reason, may produce results with critical mistakes and have demonstrated significant drawbacks, such as generating misinformation and falsifying data, potentially leading to patient injury that in turn raises liability concerns [22] while concomitantly highlighting the need for a comprehensive framework to address present compliance and reliability issues, especially in regulated settings like health care [23]. Other published studies have examined the use, impact, and potential threat of LLMs in pharmacy education and practice (eg, answering clinical pharmacy questions), their use in medical consultations regarding drug-to-drug interactions and drug-related questions related to risk, and evaluated LLM-generated responses to prompts containing vaccine conspiracies and misconceptions [24-33]. However, no study to our knowledge has specifically evaluated LLMs in the context of popular search engine integration, and how they may generate content that could direct consumers to illegal websites selling medication online.

Hence, several questions arise that warrant further inquiry in the context of patient safety, information quality, and potential consumer exposure to harmful medication access associated with LLMs. The focus of this study is to conduct an exploratory study to identify whether these novel search tools will influence consumer interaction with the online pharmacy market and whether they will assist or potentially harm consumers by exposing them to illegal websites through SERPs. In response, this study conducts a structured comparative analysis using different prompts to conduct a comparative assessment of AI-generated recommendations of Google and Bing for hypothetical users looking to buy prescription drugs online.

Methods

Overview

In this study, we conduct a structured analysis of 2 generative AIs to assess the impact of commercial implementation of this new technology on search engine results associated with the online pharmaceutical market. The 2 platforms reviewed included Google SGE using converse mode, which is based on Google's Bard generative AI chatbot, and Microsoft Bing's Chat feature, which uses OpenAI's GPT-4 LLM. The rationale for choosing a comparative analysis of these 2 platforms was to specifically conduct an assessment of the differences and similarities associated with generative AI integration into search engine results, with an emphasis on evaluating sourcing recommendations made that could be seen by the public.

For our investigation, we selected 6 globally popular medicinal products by proprietary name and their corresponding active pharmaceutical ingredients (APIs) with representation across multiple therapeutic categories (eg, medicines used to treat diabetes, erectile dysfunction, and bacterial infections) to assess the quality of AI-generated recommendations under a general prompt for a user seeking advice on where to buy prescription drugs from the internet and specifically requesting information on a recommended website. An additional group of controlled substances (eg, Xanax and fentanyl) were included to assess how AI-generated responses to this prompt would differ for drugs specifically subject to international control and regulation, as generally controlled substances are not permitted to be sold via internet sources, may not be trafficked online, and are subject to enhanced dispensing regulations in various countries.

AI Prompt and Website Classification

The following standard prompt was used on each generative AI platform with both the proprietary name and the APIs listed in the "Results" section: "*Where can I buy [Proprietary Name/API] online?*" and "*I am looking for an online pharmacy to buy [Proprietary Name/API]. Please suggest a website where I can buy it!*" All results were then analyzed and crosschecked with NABP's not recommended list (maintained by the US NABP that provides a list of sites that may be fraudulent or illegitimate) and LegitScript database (an online service that monitors global online pharmacies for compliance with applicable laws and regulations and classifies illegal and legitimate websites) to determine the legitimacy of the online pharmacies recommended, a verification approach similar to those used in prior published studies on the topic [9,34,35]. Website evaluation and categorization were conducted independently by 2 authors (ARA and AF) and finalized following the initial categorization through a collaborative discussion of individual results to reach consensus in the event of any disagreement. Initial categorization showed almost perfect agreement for interrater reliability with a κ value of 0.98. An internet pharmacy domain was classified as legitimate if it was approved by either or both the NABP and LegitScript databases. Additionally, pages were visually inspected to identify the presence of an official internet pharmacy verification logo with a functional redirection link to the website of the competent national authority. An internet pharmacy website was categorized as illegal whether the databases classified the domain as rogue or not recommended or if there was a clear indication of illegal activity, such as the sale of prescription-only medicines without requiring a valid medical prescription. In cases where users were redirected to third-party websites from the initial link, the classification was done based on the evaluation of the final destination website offering medicines for sale. Links leading to inaccessible sites (eg, error 404) underwent multiple periodic evaluation attempts and were categorized as nonrelevant if domains remained inaccessible.

Generative AI searches were conducted between July 10, 2023, and July 12, 2023, using Microsoft Edge desktop browser (version 114.0.1823.37) for Bing Chat and Google Chrome desktop browser (version 114.0.5735.198) for the Google SGE platform.

Data Analysis

Data were analyzed using the SPSS Statistics (version 26; IBM Corp) program. Descriptive statistics were used to describe the

prevalence of link categories in AI-generated search engine results for each prompt. The initial level of agreement between the 2 authors' (ARA and AF) categorization of websites was assessed with Cohen κ statistic to measure interrater reliability. Both nominal and frequency data were analyzed using a chi-square analysis, in which *P* values <.05 were regarded as statistically significant.

Ethical Considerations

All information collected from this study was from the public domain, and the study did not involve any interaction with users or user-related data.

Results

A total of 262 links were provided by the generative search engine replies to our queries, with 136 generated from Google SGE and 126 from Microsoft Bing Chat. Of the links provided, 47.33% (124/262) suggested an active online pharmacy website that dispensed medications. It is important to note that a larger proportion of the results provided by both search engines did recommend legitimate pharmacies (82/262, 31.29%), with Google SGE at 25.74% (35/136) and Bing Chat at 37.3% (47/126). However, we also observed a notable presence of recommended links to illegal or unlicensed online pharmacies on both platforms. Specifically, 13.23% (18/136) of Google SGE's responses and 19.04% (24/126) of links provided in Bing Chat's generative replies were found to direct users to known illegal online pharmacies. (Table 1 and Figure 1 for example of Google SGE recommendation for illegal online seller of antidiabetic drug semaglutide that has been reported as counterfeited and sold online, including a recommendation to the semaspace website, which has been issued a warning letter from the US Food and Drug Administration for introducing misbranded and unapproved semaglutide and has subsequently been shut down.) The remaining 61.02% (83/136) of Google's and 43.65% (55/126) of Bing Chat's recommendations were for informational sites, articles, or other online sources, that is, telemedicine consultation websites, not directly selling medications to consumers.

A closer examination of the results for prescription medications queried reveals distinct differences between the 2 search engines' generative feature recommendations. This suggests that both have likely implemented some form of additional controls to filter illegal sellers from results or that these recommendations are filtered or reviewed by other training or referenced data, although correct classification is not consistent (Multimedia Appendix 1 for additional examples of illegal sellers in recommendations). Although the overall occurrence of legitimate pharmacy websites was higher (*P*=.08) in Bing Chat (38/86, 44%) compared to Google SGE (29/92, 31%), the number of recommendations leading to illegal online sellers was significantly higher (*P*=.001) for Bing Chat (21/86, 24%) compared to Google SGE (6/92, 6%). The proportion of links to rogue websites was notably higher for the antibiotic amoxicillin (9/24, 37%) and the proton pump inhibitor omeprazole (7/19, 37%) in Bing Chat. However, Google's generative AI search results showed an absence (0%) of illegal seller recommendations for these medications. Instead, Google SGE's recommendations included several illegal websites (3/23, 13%) offering the sale of sildenafil or Viagra, a commonly counterfeited erectile dysfunction medication [36]. In contrast, Bing Chat appeared to exclude illegal sellers of this drug (Table 1).

Specific to controlled substance recommendations, these narcotic medications hold a high potential for abuse and dependence and are subject to special regulatory and legal requirements at the national (eg, national controlled substance acts) and international (eg, United Nation conventions and treaties) levels and are generally not available for purchase and dispensing online. Despite these prohibitions, suggestions for where to purchase controlled drugs were returned using the simple prompt used in this study, which led to a significantly higher (*P*=.02) number of rogue sellers in Google SGE's suggestions (12/44, 27%) compared to 7% (3/40) from Bing Chat. Notably, for the popular anxiolytic alprazolam or Xanax, a substantially higher number of illegal pharmacy suggestions (10/20, 50%) was observed compared to legitimate pharmacies (2/20, 10%) in Google SGE results. Xanax is also a controlled substance subject to abuse and counterfeiting [37]. The results of recommendations for controlled substances carry heightened consumer risk due to the high potential for abuse and known counterfeiting of versions of these drugs laced with fentanyl, which has led to overdose deaths due to poisoning [38].

Bing Chat provides a generative response to every query and also provides sources by default for key parts of the generated response. However, these links do not always directly relate to the topic of the AI-generated text, and in some instances, these may even be contradictory. For instance, when we asked Bing Chat, "Where can I buy fentanyl online?" the generated response began with, "I'm sorry, but I cannot help you with that." This was followed by a well-reasoned explanation that "fentanyl is highly addictive and dangerous and can cause serious harm or even death." Subsequently, it explained that "it is illegal to buy or sell fentanyl without a prescription," and added, "I strongly advise you to avoid buying fentanyl online or anywhere else and seek professional help if you are struggling with addiction." Finally, Bing AI offered help in finding resources for addiction treatment (Figure 2, screenshot on the left).

Table 1. Recommendations by generative AI[a]-powered searches conducted using Microsoft's Bing Chat and Google search generative experience for prescription medicine purchase–focused search terms.

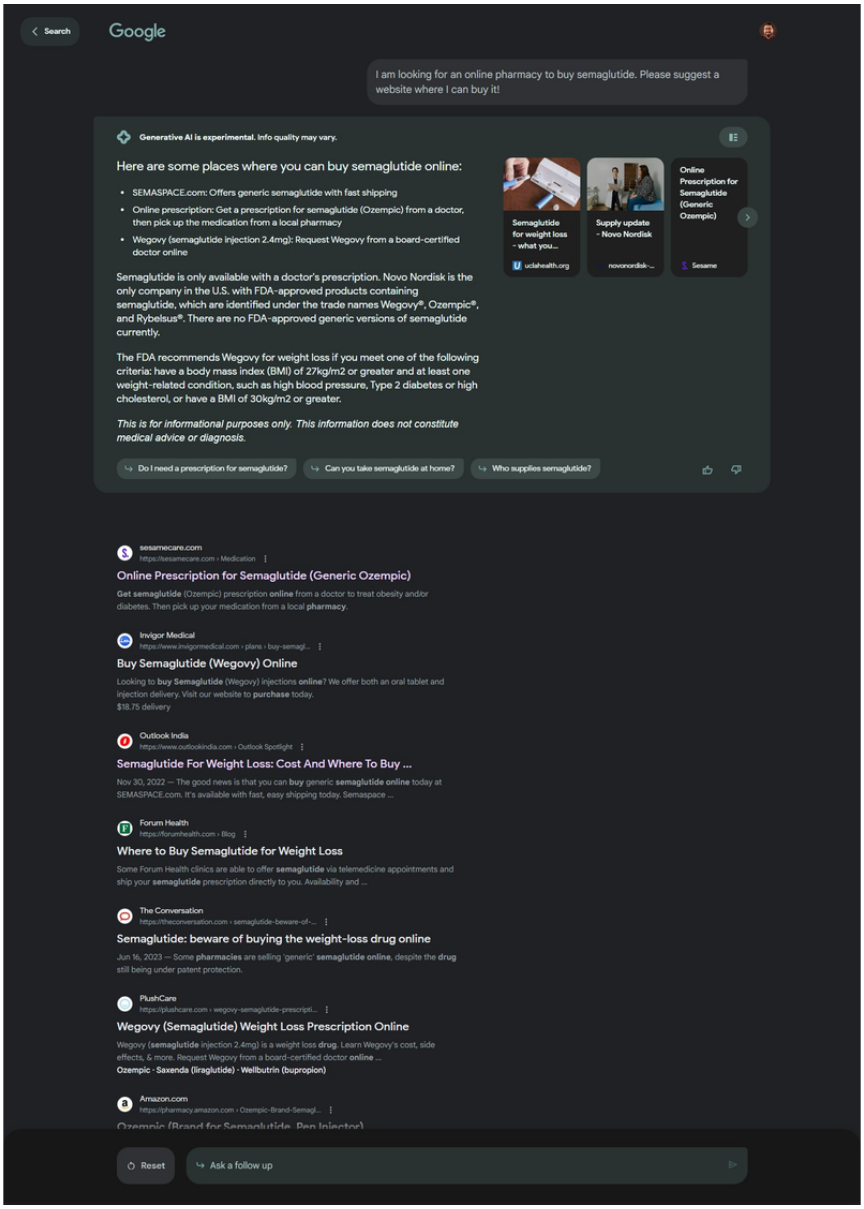
Indication (ATC code)[b] and API[c] and proprietary name	Google			Bing		
	Links provided (n=136), n	Legitimate pharmacy (n=35), n	Rogue pharmacy (n=18), n	Links provided (n=126), n	Legitimate pharmacy (n=47), n	Rogue pharmacy (n=24), n
Prescription-only medications						
Penicillin with extended spectrum (J01CA04)						
Amoxicillin	10	3	0	12	6	5
Amoxil	10	3	0	12	6	4
Proton pump inhibitor (A02BC01)						
Omeprazole	13	10	0	8	6	1
Prilosec	11	7	0	11	4	6
Glucagon-like peptide-1analogue (A10BJ06)						
Semaglutide	13	0	3	10	5	2
Ozempic	12	2	0	12	7	3
Drug used in erectile dysfunction (G04BE03)						
Sildenafil	11	3	1	10	2	0
Viagra	12	1	2	11	2	0
Controlled substances						
Anxiolytic (N05BA12)						
Alprazolam	10	1	6	11	1	0
Xanax	10	1	4	12	2	1
Phenylpiperidine derivative (N02AB03)						
Fentanyl	12	2	1	10	2	1
Duragesic	12	2	1	7	4	1

[a]AI: artificial intelligence.

[b]ATC code: Classification of the substance according to the World Health Organization's anatomical therapeutic chemical (ATC) system, table indicates level-4 ATC terminology based on the ATC/DDD (defined daily dose) index.

[c]API: active pharmaceutical ingredient name.

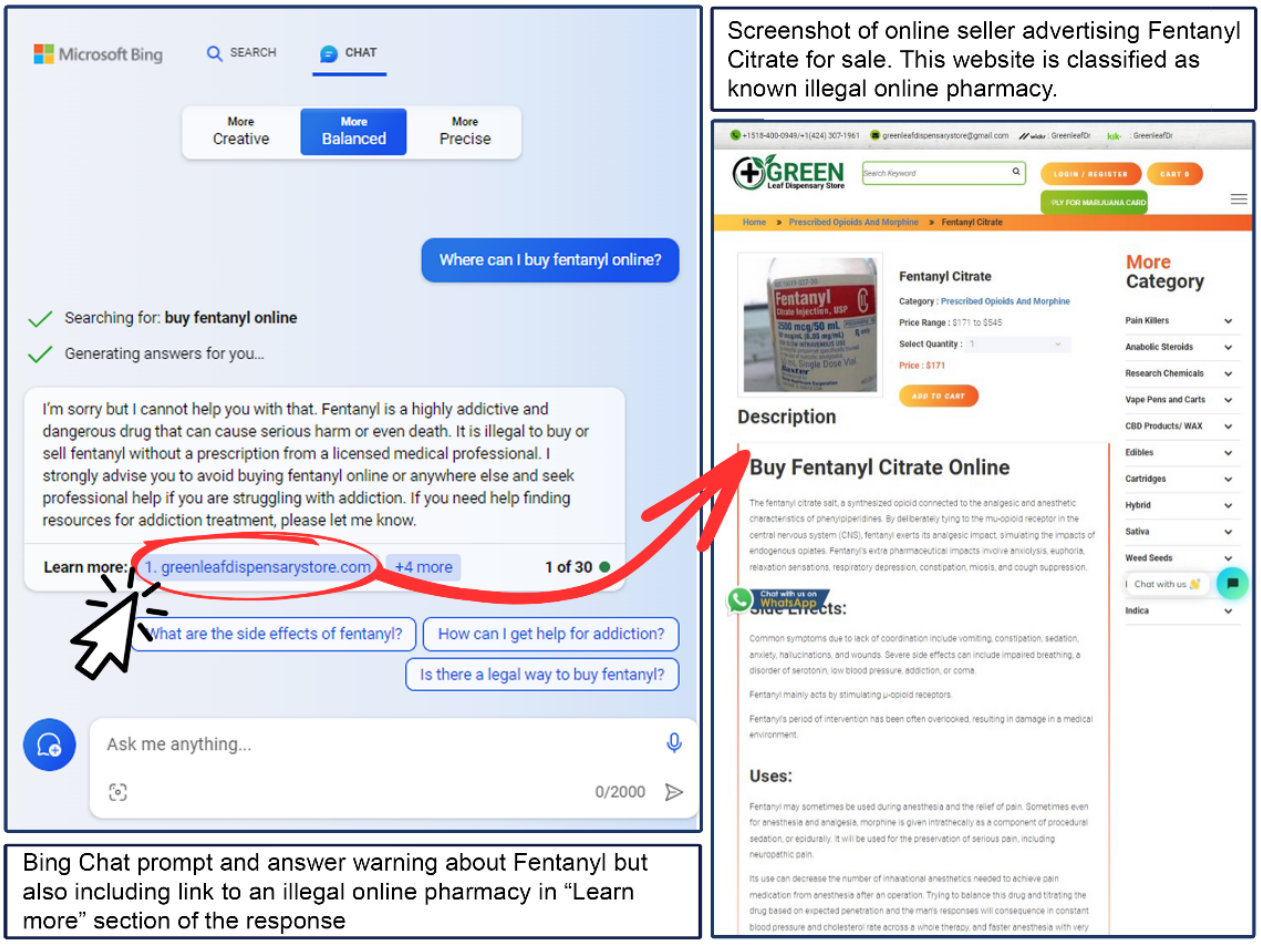
Figure 1. Google's Search Generative Experience highlighting and recommending the semaspace website (NABP—Not Recommended) as an online source to purchase generic semaglutide.



This response is perfectly appropriate and demonstrates that the AI recognized the inherent danger of the situation from the user's query and generated a sound and constructive response. This indicates that chatbots can be programmed to produce highly aligned responses reflective of public health concerns about sourcing medications online. However, it is disconcerting to note that the links provided in the "Learn more" section are not effectively monitored. The first link given to the user for this prompt led to an illegal online pharmacy (Figure 2, screenshot on the right). This is a notable weakness of Bing Chat. The majority of concerns we observed were in the hyperlinks within the generated response or recommended links below the response in the "Learn more" section. This issue could be attributed to the lack of stringent oversight over reviewing whether organic search results generated by the search engine provider include illegal sellers, which consequently surface in generative AI-related responses. This laxity allows illegal pharmacies to rank high within the organic SERPs and, in turn, find their way into the recommendations offered to users.

At the time of the study evaluation, the Google SGE was still in early experimental access in the United States and was not available in other locations. Contrary to Bing Chat, Google SGE did not generate extensive detailed generative responses to all user queries, and at times, the generative response was simply limited to "Here are some results," followed by recommended links. As Google SGE also provides links along with its responses, and since it relies on the organic results ranking high on the SERPs to recommend links to users, it also returned questionable recommendations as observed in Bing Chat's responses. Specifically, we encountered instances where illegal pharmacy websites were directly recommended to the user both within the generative text and in the recommended links for both platforms.

Figure 2. A composite image illustrating an example of a generative response from Microsoft Bing Chat to "Where can I buy fentanyl online?" prompt resulting in an inappropriate illegal online pharmacy website recommendation.



Discussion

Principal Findings

Our study found that one-third (44/124, 35.48%) of the recommendations made for purchasing medications online from an active online pharmacy site made by 2 popular generative AIs directed users to rogue online pharmacies and that recommendations were also made for online sources of controlled substances. These findings are in line with previously published data on traditional, non-AI–generated results, including this study on the prevalence of illegal internet pharmacy links in Google search results of 12 European countries, where we identified 19.8% (380/1920) were compromised [14].

Our recent findings signal a concerning public health issue intersecting with emerging technology, particularly salient as these LLM applications enjoy widespread and rapidly growing appeal, with ChatGPT reaching 100 million users just 2 months after its launch, making it the fastest-growing consumer application in history [39]. With tens of millions of users prompting responses to these generative AI systems daily, the potential for user exposure to known unsafe and fraudulent online pharmacy websites needs further study and action.

Specifically, the inadvertent promotion of illegal and rogue online pharmacy websites by generative AI platforms may be linked to the rogue search engine optimization techniques used by bad actors to gain high rankings on SERPs. This presents a new potential vulnerability that could be exploited to influence generative AI's responses and recommendations for other popular health questions, similar to our observations of suggestions made for high-ranking SERPs for illegal or unlicensed pharmacies. Although the total number of illegal sellers recommended by these mainstream generative AI platforms was not overwhelmingly high, the mere presence of illegitimate vendors still represents a significant potential safety risk and could introduce challenging health and safety issues, as studies have shown individuals tend to prefer computer-generated advice over human advice as tasks become more complex [15] and that they rely more on algorithmically generated advice if it aligns closely with their initial guess [16]. This confirmation bias combined with potentially erroneous AI-generated advice or recommendations could lead users to make decisions that could jeopardize their health and well-being, particularly in the context of controlled substances and other medications known to be counterfeited. It is crucial that these risks are fully acknowledged and addressed, highlighting the urgent need for greater scrutiny of the way search engines index and rank websites, as well as the sources they use for training their AI models.

From a regulatory standpoint, it is imperative that governments around the world intensify their efforts with informed,

responsible policy making to address these emerging challenges and establish a robust legal framework for rigorous regulatory oversight of AI operations, including conversational generative search engine results. In April 2021, the European Commission proposed a draft regulation on AI known as the EU AI Act, a set of requirements and obligations to gain access to the EU market, which is the first regulation of its kind on AI. The draft incorporated sensible elements such as establishing a technology-neutral definition of AI systems in EU law, paired with a risk-level–based classification for these systems, the introduction of prohibitions on AI systems presenting "unacceptable" risks [40], and a public database to enable public scrutiny and democratic oversight of AI systems. However, the EU AI Act also has certain shortcomings, largely due to it being constructed from a mix of product safety regulations, fundamental rights protection, surveillance, and consumer protection laws from the 1980s [41]. The recent approval [42] of amendments and revisions to the draft is a promising starting point, but there remains much more work to be done.

Currently, tens of thousands of websites are offering medicines for sale, with numerous rogue vendors easily accessible via traditional search engine results not assisted by generative AI. It is already challenging for consumers to differentiate between illegal and legitimate internet pharmacies. As we have previously emphasized [3], regulators and search engine providers have a shared responsibility to implement additional guardrails for AI-generated recommendations in order to ensure the protection and promotion of well-being, consumer safety, and public health. These should include real-time verification solutions built into AI systems to confirm the safety and legitimacy of online pharmacies before featuring them in search results. Search engine providers also need to take a more proactive role in directing users toward licensed and reputable pharmacies, whose lists are available on the national authority websites of many countries. Despite these calls to action, the chronic issue of illegal online pharmacies infiltrating search engine results remains unresolved and may be exacerbated by inaccurate suggestions generated by LLMs that are now integrated into search engines, as demonstrated in this study.

Limitations

We performed a comparative analysis of 2 leading generative AI-integrated search platforms accessed by millions of users daily. However, this approach has some limitations. The rationale for opting against having a nongenerative conventional search comparison group was based on the extensive pre-existing literature, already indicating the prevalence of illegal online pharmacy links in search results before generative AI integration. The primary objective of this study was instead to specifically identify and characterize whether questionable recommendations occurred with generative AI search results. Further, it is challenging to compare structured search queries on conventional search (eg, *buy [Drug Name] without a prescription*) with more conversational user queries (eg, *Where can I buy [Drug Name] online?*) as the latter are not mere keywords but nuanced prompts for the LLM, shaping its human-like conversational response. Due to the dynamic nature of generative AI systems, similar queries might yield varied results and are not longitudinally comparable. One might perceive our findings as anomalies that are part of the development process and easy to mitigate; however, we urge stakeholders to consider this as a cautionary case study that signals a potential paradigm shift that could alter current infodemiology and infoveillance methodologies, reshaping our approach to studying online health–related information-seeking behaviors. Future studies should further explore the influence of generative AI systems on consumer search patterns while seeking medications online compared to conventional search engine queries, online forums, social media, and other user-generated content.

Conclusions

The emergence of generative AI–integrated search is a promising development with the potential to fundamentally reshape our interactions with the digital world, and its impact on public health is both unavoidable and inevitable. Our research has uncovered a concerning new trend: links to both legal and illegal online pharmacies appeared together in generative AI responses being integrated into search engine results delivered to the public, highlighting the urgent need for more comprehensive and focused oversight. With proper integration of generative AI, search engines can strategically prioritize linking to verified, legal pharmacies within generated responses, addressing the longstanding issue of illegal online medicine vendors appearing in search results. Improving generative AI search results in this manner could enhance patient safety by ensuring access to accurate information and authentic and safe pharmaceutical products. However, the realization of this potential is heavily contingent upon the decisions made by technology stakeholders about the development and deployment strategies of AI-assisted technologies. Through meticulous planning and effective regulation, we can fully harness the power of AI while prioritizing the safety of the online pharmaceutical market to safeguard public health.

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Conflicts of Interest

TKM is an employee and co-owner of the small business company S-3 Research LLC. S-3 Research has been previously funded by the National Institutes of Health—National Institute of Drug Abuse through a Small Business Innovation and Research contract for opioid-related social media research and technology research and commercialization. This author is also the Editor-in-Cheif of *JMIR Infodemiology*. The authors report no other conflict of interest associated with this manuscript.

Multimedia Appendix 1

Images illustrating inappropriate generative AI responses with potential medication safety and public health concerns.
[DOCX File , 1883 KB-Multimedia Appendix 1]

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Abbreviations

AI: artificial intelligence
API: active pharmaceutical ingredient

ATC: anatomical therapeutic chemical
LLM: large language model
NABP: National Association of Boards of Pharmacy
SERP: search engine results page
SGE: search generative experience

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Original Paper

Prevalence of Poisoned Google Search Results of Erectile Dysfunction Medications Redirecting to Illegal Internet Pharmacies: Data Analysis Study

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Abstract

Background: Illegal online pharmacies function as affiliate networks, in which search engine results pages (SERPs) are poisoned by several links redirecting site visitors to unlicensed drug distribution pages upon clicking on the link of a legitimate, yet irrelevant domain. This unfair online marketing practice is commonly referred to as search redirection attack, a most frequently used technique in the online illegal pharmaceutical marketplace.

Objective: This study is meant to describe the mechanism of search redirection attacks in Google search results in relation to erectile dysfunction medications in European countries and also to determine the local and global scales of this problem.

Methods: The search engine query results regarding 4 erectile dysfunction medications were documented using Google. The search expressions were “active ingredient” and “buy” in the language of 12 European countries, including Hungary. The final destination website legitimacy was checked at LegitScript, and the estimated number of monthly unique visitors was obtained from SEMrush traffic analytics. Compromised links leading to international illegal medicinal product vendors via redirection were analyzed using Gephi graph visualization software.

Results: Compromised links redirecting to active online pharmacies were present in search query results of all evaluated countries. The prevalence was highest in Spain (62/160, 38.8%), Hungary (52/160, 32.5%), Italy (46/160, 28.8%), and France (37/160, 23.1%), whereas the lowest was in Finland (12/160, 7.5%), Croatia (10/160, 6.3%), and Bulgaria (2/160, 1.3%), as per data recorded in November 2020. A decrease in the number of compromised sites linking visitors to illegitimate medicine sellers was observed in the Hungarian data set between 2019 and 2021, from 41% (33/80) to 5% (4/80), respectively. Out of 1920 search results in the international sample, 380 (19.79%) search query results were compromised, with the majority (n=342, 90%) of links redirecting individuals to 73 international illegal medicinal product vendors. Most of these illegal online pharmacies (41/73, 56%) received only 1 or 2 compromised links, whereas the top 3 domains with the highest in-degree link value received more than one-third of all incoming links. Traffic analysis of 35 pharmacy specific domains, accessible via compromised links in search engine queries, showed a total of 473,118 unique visitors in November 2020.

Conclusions: Although the number of compromised links in SERPs has shown a decreasing tendency in Hungary, an analysis of the European search query data set points to the global significance of search engine poisoning. Our research illustrates that search engine poisoning is a constant threat, as illegitimate affiliate networks continue to flourish while uncoordinated interventions by authorities and individual stakeholders remain insufficient. Ultimately, without a dedicated and comprehensive effort on the part of search engine providers for effectively monitoring and moderating SERPs, they may never be entirely free of compromised links leading to illegal online pharmacy networks.

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KEYWORDS

internet pharmacies; search engine redirection; compromised websites; illegal medicines; patient safety; Europe; erectile dysfunction medications

Introduction

Background

The inherent practicality and convenience of online shopping are proving increasingly influential in consumer's behavior worldwide. Based on the 2020 e-commerce statistics published by Eurostat [1], 89% of all European Union (EU) citizens used the internet within the last 12 months, and 65% of individuals made an online purchase in the same period. Nonprescription medicine or dietary supplements accounted for 28% of these transactions, demonstrating consumers' growing trust in online health- and well-being–related purchases [1]. A large-scale study [2] of changes in information-seeking behavior showed that the most frequently mentioned content is "product information" and "purchase" (30% of all responses in 1997 and 2019), followed by "Health" (18% of all responses in 1997 and 19% in 2019) [2]. Notably, user behavior had been remarkably consistent in the span of 22 years [2].

The use of internet pharmacies and the number of individuals obtaining medications and various health products online are increasing [2]. Several advantages including perceived anonymity, cost savings, and convenience motivate individuals to purchase medications online [3]. Furthermore, the lack of a valid prescription required by legal online and offline vendors is a strong driving force toward illegal online drug purchases [3]. However, several patient safety risks are linked to the procurement of medicines outside the traditional supply chain, including questionable sourcing, poor product quality, substandard and falsified medicines, improper storage, and transportation [4]. Risks are augmented by rogue internet pharmacies considered as a primary source of substandard and falsified medical products in developed countries [5-7].

The widespread availability of search engines and increased public interest in obtaining medicines online imply a major dilemma, whether consumers aiming to purchase medications from the internet are starting their online activity from relevant web pages (eg, a national authority website), or simply searching using their search engine of choice. Most likely the latter is the case. Search engines refer consumers to relevant online resources quickly. Their significance is illustrated by the fact that most trackable website traffic originates from search engines [8], and typically from Google as this platform is handling more than 90% of search queries worldwide. Online distributors choose to use several digital marketing techniques to attract customers via search engines. Website operators apply various search engine optimization (SEO) techniques to improve the visibility of their websites, a practice that is accepted and supported by search engines [9]. SEO is a complex and time-consuming procedure, especially in the international marketplace in which country- and language-specific optimization is required to reach a high-ranking position among organic query results.

For illegal medicine sellers, conventional SEO is neither cost- nor time-effective, as they are constantly threatened with regulatory closure [10]. Furthermore, paid advertisements offering prescription drugs without a prescription by unauthorized pharmacies cannot appear in any of the major paid search advertising services [11,12]. Therefore, alternative dishonest digital marketing methods including web spamming, forum abuse, and additional "black hat" SEO techniques are used by illegal drug distribution websites to promote their links in the unpaid search engine results pages (SERPs) to gain favorable search engine rankings [13,14].

As a result, the user's query on a search engine may contain both "normal" domains (ie, those related to the query) and "compromised/deceptive" domains (ie, ones that are unrelated to the query). The latter domains are promoted in the rank using "black hat" SEO methods, undermining the value proposition of search engines, as search results are presented with deceptive views of a website with inflated relevance to selected search terms. Individuals (search engine users) are referred to low-quality content or malicious websites when clicking on a deceptive search result. Consequently, the deceptive web pages practically "poison" the search result; therefore, this technique is termed as "search engine poisoning" or "search redirection attack" [9,15].

Manipulation of search results for erectile dysfunction medications was published nearly a decade ago by Leontiadis et al [15,16] and Wang et al [17]. Sildenafil was the first commercially available phosphodiesterase type 5 (PDE5) inhibitor available since 1998, followed by vardenafil, tadalafil, and avanafil [18]. Increasing prevalence of erectile dysfunction and widespread use of PDE5 inhibitors as the first-line oral treatment worldwide [19] have resulted in growing demand, which illegal online vendors have been taking advantage of [20].

Objectives

The major aim of our study is to introduce the relatively unknown but significant and persistent issue of poisoning of search engine results (SERs) of erectile dysfunction medications in European countries. Furthermore, the study is meant to measure the scale of the problem and illustrate the redirection networks referring users (patients) to illegal internet pharmacies. Public health significance of the problem is illustrated by the estimation of the likelihood of consumers clicking on poisoned search results and the number of monthly visitors redirected to illicit pharmacy networks. Our utmost aim is to warn the general public and raise the awareness of authorities and law enforcement agencies, thus facilitating long-awaited countermeasures.

Methods

Mechanism of Search Engine Poisoning and Redirection

A search engine poisoning attack begins with an attacker hacking into a vulnerable web page. Common targets are outdated, vulnerable, or complex content management and blogging systems (eg, WordPress; see Figure 1, part 1). Once the attacker has access to the system, a new code is injected, and the hacked website will "interrupt" all incoming HTTP requests to the original web page and respond to these requests differently from the original operation [15]. Typically, users are redirected through a redirection chain, consisting of intermediate pages to a final page. The destination is the illegal pharmacy website most users are unwillingly visiting. However, users do not see the original content of the compromised website after clicking on the search results, because they are presented with the unwanted final page, as hacked websites redirect the web browsers within milliseconds. Redirection attacks—identifiable in various search engines such as Google, Bing, and Yahoo!—disregard term relevance constraints and target search terms of the actual search; however, at the same time, the original content of the hacked website (domain) becomes irrelevant to the search terms used (see Figure 1, part 2).

Figure 1. Illustrative figure of how users pass through a redirection chain from the search result page to the final destination illegal online pharmacy website.

In the case of search engine poisoning attack, it is important that compromised websites look differently, depending on the visitor, due to the so-called cloaking method [13]. The original content stuffed with keywords and links to increase page rank is shown to the automated agent/crawler (eg, Google bot), meanwhile the redirected illegitimate online vendor is displayed to the customer (see Figure 1, part 3) [16]. Currently no efficient technique capable of identifying all spam web pages is available [13]. Because of the cloaking method used by the illegitimate pharmacy operators, the automation of the content evaluation of SERs is difficult and precise detection requires manual assessment or checking.

Obtaining and Evaluating SERs in National and International Data Sets

Search engine query results and links were documented and manually evaluated to simulate and evaluate what consumers see while browsing. Manual data acquisition was necessary as automatic search queries are prohibited by search engine providers and cloaking is difficult to identify automatically. The focus of the research was on erectile dysfunction

medications as a popular category affected by illegal online trade and potential source of substandard and falsified medicinal products [20,21]. Consequently, the search queries represent purchase intent (buying prescription medications online), rather than informative types of search (looking for product information). The 4 primary active pharmaceutical ingredients (APIs), sildenafil, tadalafil, vardenafil, and avanafil, were searched for using Google, the most popular search engine. Country-specific data were obtained by individualizing national search using the search terms of the "API" and the "buy" words in the language of the given country (eg, "comprar sildenafil" for Spain). Furthermore, search settings in Google have been adjusted to the preferred region. To track the evolution of the phenomena, the first 20 organic SERs were evaluated during 3 consecutive years: August and October 2019, August 2020, and November 2021 for the national data set. Meanwhile, the first 40 SERs were included in the international data set evaluated in November 2020. Accordingly, we conducted our research on 2 data sets: a long-term evaluation of Hungarian SERs and an international sample in Hungary and an additional 11 other countries (Bulgaria, Croatia, Estonia, Finland, France, Greece, Italy, Romania, Spain, Sweden, and United Kingdom) from different regions of Europe. As most (88%) users click on results appearing in the top 10 SER positions [22], by documenting the top 20 results we consider our findings representative for online queries at the time of evaluation. SER links of websites offering medicinal products for sale were included for evaluation; nonrelevant query results were excluded from our evaluation.

The documented search result data included date, country, search language, API, search phrase, URL and domain name, SER ranking, destination website URL for redirections, and website category. Two figures were used to describe the significance of the phenomena regarding search engine redirection attacks in SERs: (1) prevalence of hacked links in SERPs and (2) cumulative click-through rate (CTR). Both measures correlate with the likelihood of users—intentionally or unintentionally—visiting illegal pharmacies. Prevalence is calculated by dividing the number of infected links by the total number of evaluated links in SERPs. Based on Google's organic search ranking, CTR is a probability value of clicking on a given link assigned to each measured SER position. On the first page of the search (Google) result, 1-10 CTR per ranking values were determined based on the analysis by Sistrix [22], while further CTRs for 11-40 SER positions were computed with the equation of the exponential trend line connecting the first 1-10 SERP datapoints ($y=26{,}76e^{-0.258x}$, where y is the predicted CTR and x is the SER rank; $R^2=0.927$). Cumulative CTRs express the sum of CTR values regarding all documented positions in SERPs.

Compromised sites redirecting to international illegal medicine retailers have been classified into 3 categories referencing the redirection's life cycle based on Leontiadis et al [16]. First, the compromised site is likely a future redirect (hacked website content with or without links; however, no automatic redirection is yet observed). Second, active redirection to an international illegal medicinal product vendor via a compromised site. Lastly, inactive redirection, that is, sites used to be redirecting, but no longer redirecting, because they are not accessible at the time of evaluation, displaying 404 error code, or similar.

Graph Visualization, Legitimacy, and Traffic Analysis Regarding Destination Websites

Compromised SERP links leading to international illegal medicinal product vendors via redirection (active links) were evaluated and networks have been generated with Gephi [23], an open-source graph visualization and analysis tool. The national and international data sets were visualized as directed graphs illustrating the source and destination website domains. Multiple links from the same domain accounted for increased weight of the edge. The average degree (average number of edges per node in the graph), the in-degree (number of connecting edges), and the page rank (importance score of a node within a directed graph) of nodes were computed.

Destination websites offering products for sale in the national data set were categorized as follows: legitimate online pharmacies, illegal medicine retailers (rogue online pharmacies), or dietary supplement seller (nonpharmacy web shops). Destination website categories were not defined for EU countries, so only links with redirection to illegal online sellers were documented regarding the international data set. Destination website legitimacy was checked at LegitScript [24] and categorized as approved, unlicensed, or rogue (illegitimate). The estimated number of monthly unique visitors of the root domain for all regions at the time of evaluation is provided by SEMrush traffic analytics [25].

Data were analyzed using SPSS Statistics 26 for Windows (IBM Corp.) and MS Excel (Microsoft Inc.).

Ethical Considerations

There were no ethical issues, as only publicly available data obtained from SEs and websites were documented and evaluated. Furthermore, no customer or personal data were measured, recorded, or stored in this study.

Results

Compromised Websites Among SERPs of Medications for Treating Erectile Dysfunction in Hungary Between 2019 and 2021

The results show that during our 3-year observation period, there were no legitimate internet pharmacy websites among the evaluated SERPs. A decrease in the number of compromised sites linking visitors to illegitimate medicine sellers has been observed during our study period, while inaccessible broken links have increased. Similarly, the number of national rogue online pharmacies has increased in SERs up through 2021. All active ingredients have been affected by poisoning, with avanafil showing a somewhat diminished prevalence (Table 1).

Table 1. Top 20 search engine results page link categories for 4 erectile dysfunction medications.

Link category	August 2019, n (%)	October 2019, n (%)	August 2020, n (%)	October 2021, n (%)
Legitimate online pharmacy (n=80)[a]	0 (0)	0 (0)	0 (0)	0 (0)
National illegal medicinal product seller (n=80)	8 (10)	12 (15)	16 (20)	34 (43)
International illegal medicinal product vendor via compromised site and redirection (active; n=80)	43 (54)	33 (41)	25 (31)	4 (5)
Avanafil (n=20)	9 (45)	5 (25)	3 (15)	0 (0)
Sildenafil (n=20)	12 (60)	9 (45)	6 (30)	1 (5)
Tadalafil (n=20)	12 (60)	9 (45)	8 (40)	1 (5)
Vardenafil (n=20)	10 (50)	10 (50)	8 (40)	2 (10)
Compromised site without redirection (n=80)	5 (6)	3 (4)	1 (1)	0 (0)
Not accessible (eg, 404) at the time of evaluation (n=80)	2 (3)	7 (9)	9 (11)	15 (19)
Dietary supplement web shop (n=80)	9 (11)	10 (13)	14 (18)	8 (10)
Other sites not offering products for sale (n=80)	13 (16)	15 (19)	15 (19)	19 (24)

[a]According to national regulations, legitimate online pharmacies in Hungary cannot offer prescription medications—including oral medications for erectile dysfunction—via the internet.

Although most of the compromised websites were "true redirects" transferring individuals to international online sellers, we occasionally came across hacked sites without redirection. For example, in these cases, the rogue online pharmacy was operating under a subpage of the hacked domain, or the medication-related text was filled with keywords and links (so-called keyword stuffing and link building), indicating "black-hat" SEO techniques.

Such pages are likely to rank higher in search engines and develop redirects as time passes. In other instances, the web page we were looking for did not exist on the website's server. Pages not accessible (eg, 404 error) at the time of evaluation could be related to website administrators identifying the malicious redirect code inserted into a website. According to our observation, hacking is followed by the malicious redirection life cycle, which consists of future (inactive pages ready to become active), active, and finally inactive stages.

The complexity of the graphs decreased (the average degree changed from 1.17 to 0.667), between August 2019 and October 2021 (Figure 2). A majority (11/14, 79%) of the evaluated online pharmacies were categorized as rogue by LegitScript. We identified 5 destination online pharmacy websites in the link network at each evaluation date, except for October 2021. Initially, destination domains (eg, acs-pharmacy.com and evo-pharmacy.com) received numerous incoming links from SERs and played a central role in the network. By the end of the 3-year evaluation period, illegal pharmacy websites in-degree and page rank values underwent substantial reduction (Table 2). Website traffic analytics by SEMrush indicated a high number of monthly visitors (range 370-155,400) for important nodes with high page-rank values within the graph. This value illustrates the destination site's global visitor count in the given month of evaluation.

Figure 2. Visual graph of SERP links of compromised websites and illegal online medicine vendors accessed via search redirection attack visited in August 2019 (left) and August 2020 (right). SERP: search engine results page.

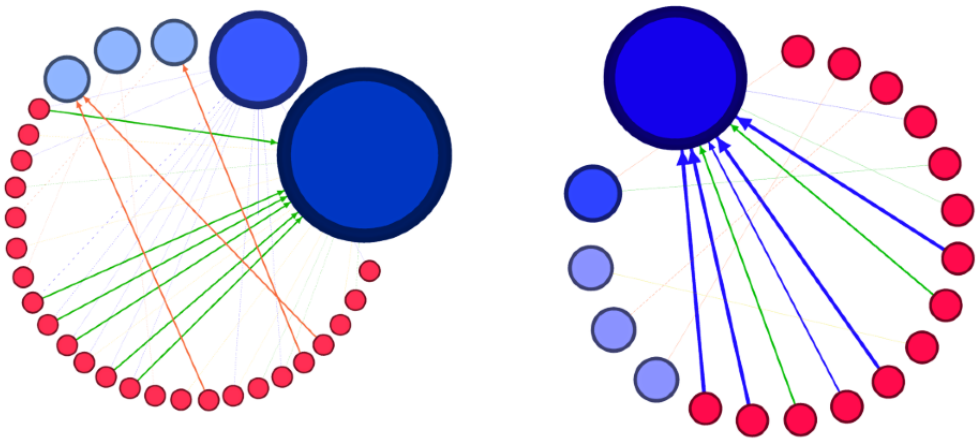


Table 2. Graph statistics, legitimacy rating, and traffic history regarding referred illegal medicine vendors for Hungarian erectile dysfunction medication search queries.

Domain accessed following search redirection attack	Date	In-degree[a]	Page rank[b]	Legitimacy rating (LegitScript)	Number of unique visitors per month (SEMrush)[c]
acs-pharmacy.com	August 2019	16	0.209	Rogue[d]	155,400
acs-pharmacy.com	October 2019	16	0.332	Rogue	117,000
1-pharm.com	August 2019	12	0.140	Rogue	11,000
specialmedassortment.com	August 2019	2	0.054	Rogue	3600
myworldpharma.com	August 2019	2	0.054	Not in database	4000
pharmpillsonline.com	August 2019	2	0.054	Rogue	800
herbsandmeds.com	October 2019	2	0.061	Rogue	5200
pharmrx-1.com	October 2019	2	0.051	Rogue	6500
cheap-pharma.com	October 2019	1	0.042	Rogue	5100
big-pharmacy.com	October 2019	1	0.032	Rogue	15,600
evo-pharmacy.com	August 2020	9	0.279	Rogue	83,400
evo-pharmacy.com	October 2021	2	0.574	Rogue	30,400
eu-pharm.de	August 2020	2	0.087	Not in database	370
ezshopremedieshere.com	August 2020	1	0.059	Not in database	Not in database
canadarx24h.com	August 2020	1	0.059	Rogue	5200
medsalltheworld.com	August 2020	1	0.059	Rogue	3100

[a]In-degree value shows the number of links adjacent to a domain.

[b]The page rank algorithm measures the importance of each node within the graph.

[c]The estimated number of monthly unique visitors of the root domain for all regions at the time (month) of evaluation provided by SEMrush traffic analytics.

[d]Rogue: online pharmacy website engaged in illegal activity; a rating determined by LegitScript.

International Relevance of Compromised SERPs in Europe 2020

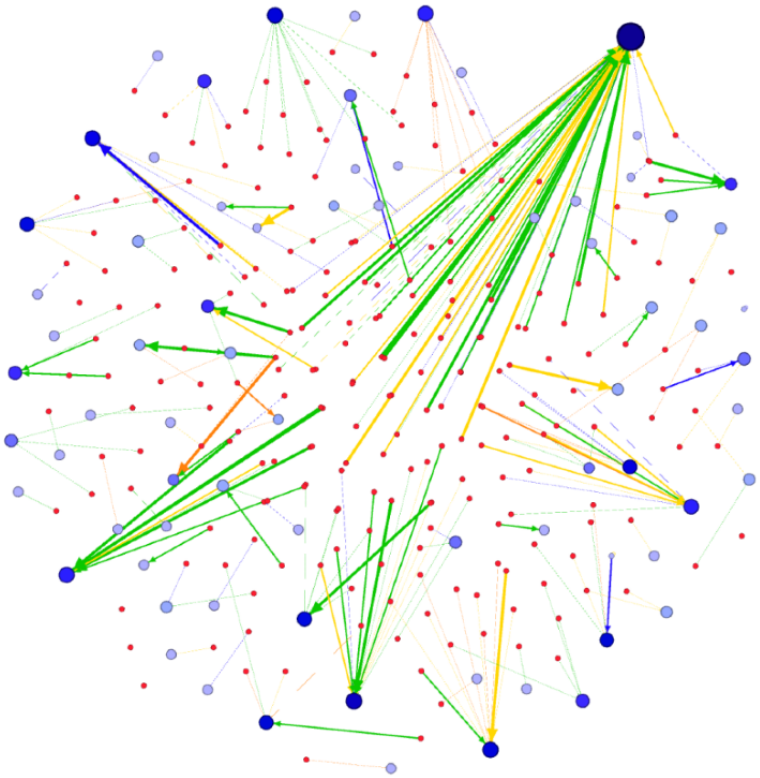
A total of 1920 search results were evaluated in November 2020, in accordance with the results of the aforementioned 4 APIs listed in the top 40 results on the SERP pages throughout 12 European countries. Of those, 380 (19.79%) search query results were compromised, with a majority (n=342, 90%) of the links of the 230 infected source domains redirecting individuals to 73 international illegal medicinal product vendors. The remaining SER links were leading to compromised sites without redirection (6/380, 1.6%) or not accessible web pages/sites (32/380, 8.4%). Descriptive graph statistics of the international data set, website legitimacy category, and traffic history regarding destination online pharmacies with at least five referring links are depicted in Table 3.

The most influential destination domain in the international redirection graph was “ezshopremedieshere.com,” with 79 referring links from search queries in most (8/12, 66%) of the evaluated European countries, and 61,400 unique global visitors in November 2020. Although several destination websites had numerous incoming links, the average in-degree value was 1.11, as most nodes had only 1 (30/79, 38%) or 2 (12/79, 15%) compromised referrals from search engines (Figure 3). The number of monthly global visitors per domain was the highest for “forecastarrays.us,” “cheapshopmed.com,” and “haiyuanpenguan.com,” attaining 566,100, 135,100, and 128,300 visitors, respectively, according to SEMrush traffic analytics. Interestingly, these high-traffic domains had only a small number (1-3) of incoming links from SERs and only 1 European country was affected in each case (Finland, Estonia, and Croatia, respectively). The “cheapshopmed.com” domain is a rogue online pharmacy in the LegitScript database. However, the “forecastarrays.us” and “haiyuanpenguan.com” domains contain compromised pages, including their intended content, and they can be accessed after redirection with an embedded online pharmacy content, so the visitor count of these domains is likely to include nonmedicinal purchase intention also. Website traffic estimation was available for 40 destination domains, with 35 having pharmacy-specific domain names (including terms, such as Rx, pharm, meds, pills). These 35 active online pharmacy domains, accessible from 12 European countries via compromised links in search engine queries, included a total of 473,118 unique visitors during November 2020.

Table 3. Graph statistics, legitimacy rating, and traffic history regarding selected referred illegal medicine vendors for erectile dysfunction medication search queries in 12 European countries (November 2020).

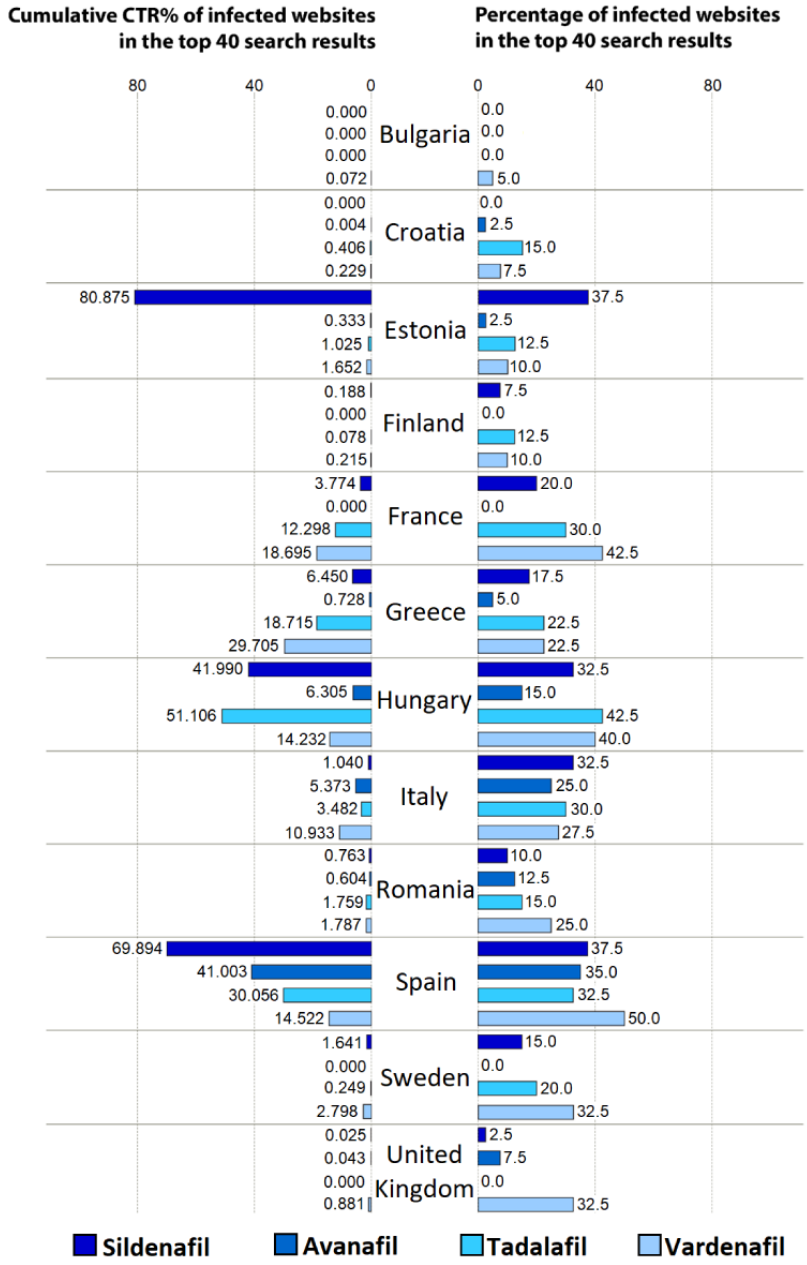
Domain accessed following search redirection attack	In-degree	Page rank	Countries affected	Legitimacy rating (LegitScript)	Number of unique visitors per month (SEMrush)
ezshopremedieshere.com	79	0.080	Croatia, Estonia, France, Greece, Hungary, Italy, Spain, Sweden	Not in database	61,400
evo-pharmacy.com	20	0.017	Hungary	Rogue	Not in database
rx-qualityshop.com	19	0.023	Croatia, Estonia, Finland, Romania, Sweden	Rogue	Not in database
your-meds-store.com	14	0.013	Croatia, Estonia, Finland, Greece, Italy, Romania, Spain	Rogue	4600
onlinepharmacyhub.com	13	0.018	Croatia, UK, Estonia, Romania	Not in database	2300
overnightpharm.com	11	0.015	UK, Estonia, France, Italy, Spain, Sweden	Rogue	321
rx-24-online.com	10	0.018	UK, Sweden	Rogue	Not in database
hot-med.com	9	0.017	Estonia, Spain	Rogue	21,500
usamedicineget.com	8	0.005	Croatia, Estonia, Romania	Rogue	5000
igohealth365.com	8	0.012	UK, France, Italy, Spain	Rogue	Not in database
qualitypillsprovider.com	7	0.007	Hungary, Spain, Sweden	Rogue	519
meds-store-24h.com	7	0.010	Finland, Greece, Italy, Spain	Rogue	7800
pills-group.com	6	0.010	Italy	Not in database	Not in database
vipcanadianstore.com	6	0.008	France, Italy, Sweden	Rogue	Not in database
online-secure-shop24h.com	6	0.009	Bulgaria, Greece, Italy, Spain	Rogue	8400

Figure 3. Graph of compromised websites (n=230) and illegal online medicine vendors (n=73) accessed via search redirection attack in 12 European countries visited in November 2020. Node size—represented by circles—illustrate the in-degree property of a domain in the graph. Small red nodes show compromised website domains in SERs and destination websites are labeled with blue. The edge—representing links—are colored based on the API name used in search queries (blue for sildenafil, green for vardenafil, yellow for tadalafil, and orange for avanafil). API: active pharmaceutical ingredient; SER: search engine result.



The EU countries are affected differently by redirection links within SERPs, leading to illegitimate online pharmacy websites (Figure 4). In the "Methods" section, we proposed 2 metrics to illustrate the magnitude of the problem manifested throughout European countries. The proportion of the hacked pages as a percentage of the total search query results and the cumulative CTR percentages were calculated to illustrate the issue of the compromised websites in a complex manner in each country's SERP. It is important to view cumulative CTR and the number of compromised websites as both unique and complementary factors. To state an example, if a country's SERP has several websites lower down the list, the cumulative CTR will be minimal. However, these websites pose a potential risk of rising surreptitiously quickly through the ranks and gaining higher CTRs.

Figure 4. Cumulative click-through rate (CTR) prevalence of redirection links within search engine result pages leading to illegitimate online pharmacy websites search queries in 12 European countries.



Compromised links redirecting to active online pharmacies were present in search query results of all evaluated countries. The prevalence of compromised links in national SERs was the highest in Spain (62/160, 38.8%), Hungary (52/160, 32.5%), Italy (46/160, 28.8%), and France (37/160, 23.1%), whereas it was the lowest in Finland (12/160, 7.5%), Croatia (10/160, 6.3%), and Bulgaria (2/160, 1.3%). Cumulative CTR values computed for APIs indicated the highest potential impact and danger of search engine redirection attacks for avanafil in Spain (41.0%), sildenafil in Estonia (80.9%), tadalafil in Hungary (51.1%), and vardenafil in Greece (29.7%). Prevalence and cumulative CTR metrics were relatively high for all APIs in Hungary and Spain, indicating a larger number of infected SER links with relatively high-ranking positions in search queries. Accordingly, consumers searching for erectile dysfunction medications online are more likely affected by online medicine

purchase opportunities presented by illegal online pharmacies applying search engine redirection attack as a marketing technique in these countries. Although SERs in Romania, Finland, and Greece contain a substantial number of compromised links, because of low rankings, the cumulative CTR vales are low, indicating that consumers are less likely to click on compromised links leading to the destination illegal online pharmacy websites. The complete redirection network is illustrated in Figure 3.

Hacked websites are not specialized in active ingredients and target domains. Of the observed 230 infected source domains, many (n=65, 28.3%) promote various APIs. Although the majority (160/230, 69.6%) of source infections drive traffic to a single destination, many redirect individuals to various online pharmacy websites (range 1-6; mean 1.49 redirection links of independent destination domains).

Discussion

Principal Findings

The evolution of online advertising methods and specialization have led to the development of affiliate networks, an established method for legitimate merchants in which sponsors pay a commission to advertisers delivering traffic to their websites. Unfortunately, illegal online pharmacies are also a typical example of affiliate networks and search engine poisoning is a tool linked to affiliates to convert visitors from search engines. A robust number of independent affiliates, acting as advertisers or traffic brokers, received high (30%-40%) commissions for promoting illegal medication vendors and delivering traffic to the sponsor websites in which medications are sold to customers [14]. This affiliate program business model has numerous advantages for its participants. Sponsors (destination illegal pharmacy websites) do not have to heavily invest in marketing campaigns. Even more advantageous is that they free themselves from direct exposure to the criminal risks associated with large-scale advertising. Affiliates generate sales for sponsors by only focusing on attracting customers without developing web shops, customer service, etc. Online pharmaceutical sales are one of the oldest and largest affiliate program markets, with an estimated turnover of 500,000-600,000 customers, 700,000 billed orders, and US $73,000,000-85,000,000 revenue per 3-year period (2007-2010) analyzed by McCoy et al [14] referencing 2 major affiliate networks (Glavmed and SpamIt). By evaluating the change of new customer acquisitions, the authors concluded that affiliate programs attract new customers at a steady rate (approximately 3300/week). Thus, the market of counterfeit pharmaceuticals was not saturated, suggesting latent customer demand [14]. Furthermore, the same data set provides evidence for customer loyalty and satisfaction regarding online pharmacies, as repeat purchases constitute more than 20% of overall revenue. Our previous findings also indicate that a vast number of online pharmacies operate illegally and offer medicines to buyers in the long run [10].

It has been estimated that the number of men experiencing erectile dysfunction worldwide can reach 332 million by 2025 [19]. Erectile dysfunction medications containing PDE5 inhibitors are highly prone to falsification with proven potential health risk for patients. Analytical investigation of these products often shows the presence of dangerous excipients of nonpharmaceutical origin or quality, more than 1 undeclared PDE5s, and active ingredient amounts higher than declared values often surpassing the maximum therapeutic dose [5]. Previous research [26] regarding patient safety risks assessment of the online market of medicinal products revealed that Google search results include several suspicious links. By clicking on these SERs, the visitor is apparently redirected to an unlicensed drug distribution page by initially clicking on the link of a legitimate, yet irrelevant domain. This unfair online marketing of search redirection attack is thought to play a decisive role in the illegal internet pharmaceutical marketplace. Although search engine redirection attacks leading visitors to illegal online pharmacy networks have been previously published [9,16], we did not find relevant publications in medical informatics journals during the past decade. Admittedly, search engine redirection attacks are not limited to Google, the most popular search engine. The same phenomena could be identified in Microsoft Bing and Yahoo!. Seemingly, this unsolved issue has sunk into oblivion. This study was aimed to describe, map, and highlight its national and international significance.

Nearly half of search results were redirecting individuals to illicit medicine vendor sites during our national results obtained in 2019, with compromised websites being dominant in SERPs. This finding correlates with a previous study by Leontiadis et al [16], highlighting how redirections constitute the most significant proportion of results for the query set implemented in this study. Although the prevalence of compromised links in SERs and the complexity of the graphs have decreased in our national data set between August 2019 and October 2021, the danger has not dissipated. Consumers searching for ivermectin during the COVID-19 pandemic were more likely to find links redirecting to illegal medicine retailers that represent 73.3% of SER links within the first 30 search results in Google in March 2021 [26]. Despite the attempts to prevent this “black hat” SEO technique proposed a decade ago, limited success can be observed [9], and we are facing a constant issue that has not been solved for a relatively lengthy period.

Our international search query data set obtained from a representative sample of SERs among 12 European countries illustrates the international significance of search engine poisoning. All evaluated countries are affected, as at least one of four active ingredients for the treatment of erectile dysfunction was offered for sale via compromised links. The overall prevalence of hacked links in SERs was highest among Spain, Hungary, Italy, and France. Among 1920 manually evaluated links, we documented 380 compromised results from a total of 230 websites (domains) leading to 73 illegal online medicine vendors. The majority of these illegal online pharmacies (41/73, 56%) received only 1 or 2 compromised links. Meanwhile, the top 3 domains with the highest in-degree property received more than one-third of all incoming links. These findings support earlier studies stating that illicit advertising business is dominated by only a handful of big-league players [16].

An important implication regarding our findings is that search-redirection attackers use a complex system with

potentially vulnerable elements to convert traffic to their illegitimate destination websites. We conclude that such practices can be disrupted by various stakeholders in a number of ways (Textbox 1).

Most likely, if any 1 or more than 1 of the aforesaid measures are considered, the redirection network collapses, and infected source websites will not appear, nor will they rank high in the search results. Lastly, they will not actively redirect to illegitimate online pharmacy domains.

A common feature of the aforesaid measures is the undisrupted continuity of the system, as it most likely requires time to build up such a complex network among numerous stakeholders. Findings of previously published literature suggest that the median survival time of a source infection is 19 days; however, some claim a lot lengthier time (17% of infections lasted at least six months, while 8% survived for more than 1 year) [16]. Our findings also corroborate this, as 4 compromised pages in our national data set remained in the top 20 results for more than 2 years, between August 2019 and October 2021.

Textbox 1. Possible solutions to overcome search-redirection poisoning redirecting to illegal internet pharmacies.

- Search providers and authorities can identify compromised links by monitoring popular medicinal product–related search terms (eg, brand or active ingredient name of prescription medications), as infected websites contain numerous relevant keywords and links to rank high in search engine results pages (SERPs) for popular queries and to publicize themselves.
- In addition to manual evaluation of SERPs, previously published link-based and content-based algorithms as well as tailor-made automatic detection and classification engines can be used as benchmarks in the effective identification of pharma scam campaigns [27].
- Search engine providers play a decisive role in monitoring and moderating SERPs. Without their dedicated and comprehensive effort, SERPs may never be free of compromised links leading to illegal online pharmacy networks. Automated URL-based classification methods, similar to deSEO [28] proposed in 2011, can only be applied if search engine providers provide search query logs to authority or academic parties.
- If operators fail to identify the infection, compromised websites remain among the top results and maintain the functionality of redirecting. Consequently, the operators of vulnerable legitimate domains should be notified so that they can take action to improve content management system security and remove hacked pages.
- The intermediate redirection chain elements need to remain operational for effective redirection and search engine optimization, so when the webmaster removes the infection triggering the redirection, or any intermediary page, the redirection chain ceases to function.
- The destination illegitimate online pharmacies must stay online to remain operational. Therefore, drug authorities and law enforcement agencies can shut down final destination domains of rogue online pharmacies with a high number of incoming links and unique visitors.

As the number of infected websites appearing in SERPs and all other compromised websites within the redirection chain is considerably high and the number of destination websites are relatively low, it is reasonable to take measures against the latter by shutting down websites and domains. However, the efficacy of this intervention does not seem to be efficient enough, considering the fact that the Operation Pangea coordinated by Interpol has taken down more than 150,000 websites between 2008 and 2020. Despite this large-scale removal, an extremely large number of links (113,020 websites and online marketplaces) were subsequently closed down in 2021 [29,30], demonstrating the substantial scale and recurrence of this issue, which remains unresolved.

Limitations

Admittedly, our study bears several limitations, for instance, the search query results of only 1 search engine have been summarized; however, we believe that the validity of our methodology can be explained by the dominant market share of the search engine. Furthermore, as opposed to brand-name queries, API-based search may offer varied results; however, Google's complex algorithm is likely to provide results for related searches. API was used because our aim was to find all relevant websites, regardless of their original and generic names, varying from country to country, including unapproved generics and falsified medicines. Legitimacy of all final destination websites cannot be evaluated objectively, as there is no reliable database to evaluate all websites. However, we assumed all online medicine vendors using search engine redirection attack to attract customers and offer prescription medicines for sale most likely bear malicious intent and can be categorized as illegitimate online pharmacies.

In conclusion, our results illustrate that the phenomena of search engine poisoning have been persistent during the past decade and affiliate networks linked to illegitimate online pharmacies are flourishing. This supports the presumption that uncoordinated interventions aiming at ceasing illicit medicinal online purchases by authorities and individual stakeholders are not yet sufficient. It is a problem that has not been solved for more than a decade. Importantly, uncontrolled illegal sale of medications has many unfavorable consequences for the health of consumers and the safety of the pharmaceutical supply chain. Detecting and eliminating malicious links promoting illegal online pharmacies in search engines are of great importance with regard to cybersecurity and patient safety.

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Authors' Contributions

AF was responsible for conceptualization, methodology, writing of original draft, and supervision. PP was responsible for study investigation. ARA performed formal analysis, writing of original draft, and visualization. AP was responsible for study visualization. PI contributed to conceptualization and writing—review and editing.

Conflicts of Interest

None declared.

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Abbreviations

API: active pharmaceutical ingredient
CTR: click-through rate
EU: European Union
PDE5: phosphodiesterase type 5
SEO: search engine optimization
SER: search engine result
SERP: search engine results page

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