

The dangers of sexual enhancement supplements and counterfeit drugs to “treat” erectile dysfunction

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Abstract: Counterfeit phosphodiesterase-5 inhibitors (PDE-5i) are an increasing problem. Already in widespread use, the market for PDE-5i is steadily growing as the population ages. Counterfeiters are taking advantage of this growing market by developing illicit and counterfeit PDE-5i products. Many factors are contributing to the rapid growth of the illicit market, such as the low risk of prosecution, potentially high financial reward, and ease of distribution via Internet pharmacies. Consumers of illicit PDE-5i often do not realize they are using counterfeit products and placing themselves at an unnecessary health risk. Others seek to bypass the legitimate healthcare system due to either embarrassment of the underlying condition or desire for cheaper alternatives. However, taking illicit PDE-5i may harm consumers directly, as many illicit products contain detrimental contaminants and inaccurate amounts of the active ingredient without the appropriate warnings. Bypassing the legitimate healthcare system also endangers consumers indirectly, as erectile dysfunction (ED) is often associated with other medical comorbidities that patients should be screened for. Furthermore, PDE-5i can have potentially dangerous interactions with other pharmaceuticals that are rarely warned against with counterfeit PDE-5i. This communication reviews the literature regarding counterfeit PDE-5i, and summarizes both the scope and dangers of the illicit PDE-5i market.

Keywords: Counterfeit; phosphodiesterase-5 inhibitors (PDE-5i); erectile dysfunction (ED); black-market; supplements

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What is a counterfeit drug?

The counterfeit drug market is a nebulous and constantly evolving entity that has become increasingly difficult to define and quantify. In 2009, the World Health Organization (WHO) defined a “counterfeit medicine” as one “*which is deliberately and fraudulently mislabeled with respect to identity and/or source.*” However, many in the organization have disputed this definition of counterfeit medicine, and there appears to be no universally agreed upon definition amongst member states of the WHO. Counterfeiting can apply to both branded and generic products. This can include products with bona fide

ingredients, but with insufficient or excessive quantities, products with the wrong ingredients, or products with deceptive packaging. Currently, the WHO is using the term “*Substandard, Spurious, Falsely labeled, Falsified, and Counterfeit (SSFFC)*” for medical products until a new definition is agreed upon (1). For the purposes of this paper, the term “counterfeit” will be used to encompass all forms of SSFFC medications.

Is counterfeiting a significant problem?

Regardless of the definition, drug counterfeiting has

become a global problem. In addition to the intellectual property rights that counterfeiters violate, the products they make can place consumers in danger. Legitimate pharmaceuticals must pass vigorous standards and undergo large, randomized trials before being formally approved for the public. Then, all sanctioned medications are manufactured under heavily monitored conditions. Counterfeit medications bypass all these safeguards (2).

Despite these potential dangers, the market for counterfeit products has grown astronomically. In 2006, the WHO estimated that 10% of drugs worldwide were counterfeit, with the figure at 25% in developing countries, and as high as 50% in certain African and Asian countries (3). However, the WHO has since become less definitive in estimating the scope of the problem, as there is an inherent difficulty in quantifying counterfeit products, which have become increasingly sophisticated and difficult to differentiate from genuine medicines. In a 2016 statement, the WHO stated that *“there are many estimates of the scope and scale of the market in counterfeit medical products, but little validated evidence to underpin those estimates.”* Furthermore, the WHO has withdrawn all of their previous estimations of the scale of the problem (1). Regardless, it is clear that counterfeit medications have reached an industrial level scale. In a private study, 2,177 incidents of pharmaceutical crime involving seizures or police raids were reported in 2015, with 53% of them classified as commercial involving greater than 1,000 dosage units (4). These numbers do not even account for individual distribution and consumption of illegal pharmaceuticals, not to mention the illegal operations that escape detection. Some sources estimate that the market for counterfeit medications ranges between 75 and 200 billion dollars (5,6).

The market for counterfeit phosphodiesterase-5 inhibitors (PDE-5i)

The large market for counterfeit medications is not equally distributed in size or class of medications worldwide. It is largest in poor and developing countries, with the size of the market being inversely proportional to the amount of regulation. The proportion of falsified drugs ranges from 1% in industrialized countries that have a well-regulated and controlled drug market to as high as 60% in some developing countries (6). However, even in these well-regulated countries, the market for counterfeit PDE-5i has grown. Globally, antibiotics comprise the largest class of counterfeit medications, but in Europe, PDE-5i are

the most commonly counterfeited medicines (7). In fact, for PDE-5i, the illegal market in industrialized countries approaches the size of that in developing countries. Between 2004 and 2008, 35.8 million counterfeit sildenafil tablets were seized in Europe, which is 7 times greater than the amount of all other counterfeited Pfizer products combined. Two separate analyses in Europe estimated that 0.6 to 2.5 million men are being exposed to illicit sildenafil compared to approximately 2.5 million users of legal sildenafil (8). However, the true scope of illicit PDE-5i use is difficult to estimate. In one study attempting to estimate illicit sildenafil use, concentrations of sildenafil and sildenafil metabolites were measured in sewage treatment centers in the Netherlands. The total sewage load was back calculated to estimate total sildenafil consumption, and it was found that greater than 60% of identified sildenafil was not accounted for by legal prescriptions (9).

Why is there such a large market for counterfeit PDE-5i?

Many factors contribute to the disproportionately large market of counterfeit PDE-5i. First, there are high economic gains to be made. Erectile dysfunction (ED) is a common problem and increases in incidence as men age (10). According to the Massachusetts Male Aging Study, 52% of men aged 50–70 have some degree of ED, a number that increases to upwards of 70% in men older than 70. As the world population ages, there is a larger potential market forming. Furthermore, the cost of a single PDE-5i pill is priced upwards of \$20–30. With the low cost of base materials and the high cost of pills, the profit margin for creating sildenafil is approximately 2,000 times that of cocaine. Meanwhile, while the punishment for buying 1 kilo of cocaine would be a minimum of 5 years to a maximum of 40 years in jail, the punishment for buying 1 kilo of sildenafil is typically 3 years (11). With such significant profits to be made at a relatively low risk, there is a tremendous incentive for counterfeiters to tap into the growing market for PDE-5i.

Besides the high profit margins, the underlying characteristics of consumers of PDE-5i make it a prime target for counterfeiters. There is an associated embarrassment of the underlying condition of impotence that leads patients to seek alternative means of obtaining PDE-5i (12). In two large surveys, 23–32% of PDE-5i users had no prior interactions with healthcare professionals (13,14). Predictive factors for obtaining PDE-5i while avoiding interaction

with healthcare professions were embarrassment and the perception that it would be cheaper to get the medicine through alternative means. Furthermore, many users of PDE-5i are recreational users. In those same surveys, 16–36% of reported users did not report ED (13,14). These statistics speak to the underlying idea that users believe PDE-5i are harmless and that they can be self-prescribed, with no negative consequences. Furthermore, PDE-5i use is a relative luxury. Increasing household income and availability of a sexual partner positively correlate with their legal use (15). These patients with higher socioeconomic statuses having the resources to pay for pharmaceuticals out-of-pocket, combined with the stigma of ED, creates an environment ripe for an illicit market.

Internet pharmacies have made it easier for PDE-5i users to bypass the healthcare system, as 16.5% of PDE-5i users obtained the medicine through the Internet (13). Of these users, 68% did so without a prescription, as patients often do not realize that they are getting false and possibly dangerous products, and 60% of these users believed they received the same product as from a legitimate pharmacy (13). A simple Internet search for “internet drug store” revealed 6.4 million hits and 7,000 Internet pharmacies. Of these “pharmacies,” only 4% were in compliance of the Verified Internet Pharmacy Practice Sites (VIPPS) program (16). Many of these pharmacies are based in foreign countries and are poorly regulated. In a random search of Internet pharmacies for Viagra (Pfizer, New York City, New York, USA), 90% of these Internet pharmacies offered illegal “generic Viagra.” No pharmacy required a prescription or a health screening survey for purchase, and the products lacked product information, appropriate safety warnings, and genuine Viagra formulations. In fact, only 18% of Internet-ordered “Viagra” was genuine (17). The ease and convenience of purchasing counterfeit PDE-5i products via the Internet have contributed to the growth of the illicit market.

While the market for counterfeit pro-erectile medications is partially driven by the cost of prescription drugs, this reality could soon change. As the patents for PDE-5i will be expiring soon, it is conceivable that the cost of these drugs may be reduced significantly. This in turn could lead to a decreased demand for cheaper alternative counterfeit options. These dynamics are already evident with many pharmacies advertising for generic sildenafil (20 mg), used for pulmonary hypertension, at a significantly lower cost. Furthermore, as mentioned earlier, embarrassment with potency issues leads patients to avoid physician visits. PDE-5i have been shown to be safe medications and may

ultimately be available over the counter. This strategy could help ease patient concerns and re-invigorate the PDE-5i market.

Why are counterfeit PDE-5i dangerous?

In order to understand the dangers of PDE-5i, it is important to first understand how PDE-5i are used. PDE-5i are effective in treating ED of many etiologies, and are currently both the first line and mainstay treatment option. Studies have suggested that PDE-5i are also effective in treating premature ejaculation, decreasing refractory time post-ejaculation, and diminishing lower urinary tract symptoms (18). They are an inhibitor of phosphodiesterase, which is an enzyme in the biochemical cascade of erection initiation. In the normal erection process, vascular endothelium releases nitrous oxide, which activates guananyl cyclase to convert guanosine triphosphate to cyclic guanosine monophosphate (cGMP). cGMP then acts on protein kinase G to open calcium channels that leads to vasodilation and an erection. Phosphodiesterase-5 acts to convert cGMP to GMP, which interrupts this chain and leads to detumescence (19,20). Thus, PDE-5i prevent cGMP from being metabolized, leading to sustained vasodilation.

There are numerous known side effects of PDE-5i, some of which may be life threatening. As PDE-5i are active in the vasodilation pathway, there is a risk of profound hypotension and syncope with concurrent use of nitrates and alpha-blockers. The use of nitrates is an absolute contra-indication to PDE-5i use and the use of alpha-blockers is a relative contraindication. There is no current pharmacologic antidote to these interactions (21). Other side effects include headache, dyspepsia, flushing, myalgia/back pain, visual disturbances, and nasal congestion. Many of these side effects occur because there is cross-reaction with other phosphodiesterase types located throughout the body (18,22). PDE-5i are metabolized almost exclusively by the cytochrome P 450 system in the liver, specifically Cytochrome P4503A. Concurrent use of CYP 3A inhibitors or inducers can significantly alter the concentration of serum PDE-5i changing the side-effect profile, effectiveness of the medication, or severity of drug interactions (21). Examples of commonly prescribed medications that have interactions with PDE-5i are included in *Table 1*. Before PDE-5i are prescribed, patients must be evaluated for potential drug interactions and warned of the absolute contra-indications.

Table 1 Common medications and dietary supplements with interactions with phosphodiesterase-5 inhibitors (PDE-5i)

Substance	Class	Interaction
Sublingual nitroglycerin	Nitrate	Hypotension
Phentolamine	Alpha-blocker	Hypotension
Ketoconazole	Anti-fungal	CYP3A inhibitor
Indinavir	Anti-retroviral	CYP3A inhibitor
Clarithromycin	Antibiotic	CYP3A inhibitor
Grapefruit juice	Dietary supplement	CYP3A inhibitor
Amiodarone	Antiarrhythmic	CYP3A inducer
Rifampin	Antibiotic	CYP3A inducer
Ginko	Dietary supplement	CYP3A inducer
Fluoxetine	Antidepressant	CYP3A inducer

There is also an indirect risk of missing potential medical conditions in patients that bypass the healthcare system to purchase illicit PDE-5i. It has been well documented that ED is associated with significant medical comorbidities including cardiovascular disease, diabetes, metabolic syndrome, hypertension, and hyperlipidemia (23). The Second Princeton Consensus on sexual dysfunction and cardiac risk stated that all men with ED, even in the absence of manifesting cardiac symptoms should be regarded as having potential risks for cardiovascular disease (24). Currently, evidence suggests that ED is not only correlated with cardiovascular disease due to shared medical comorbidities, but is, in fact, an independent risk factor for cardiovascular disease. Thus, all men with vasculogenic ED should undergo cardiac risk stratification and risk factor management (25). In an analysis of 24,708 patients receiving a PDE-5i, 70% had an underlying medical diagnosis, with 50% of these patients having vasculogenic disease. Furthermore, 11.5% of patients being evaluated for a PDE-5i prescription had a new underlying disease detected (26).

What is in counterfeit PDE-5i?

The most detrimental problem with counterfeit PDE-5i is that the content is unregulated. In 2009, United Kingdom authorities seized 2,383 samples of counterfeit Viagra and forwarded them to Pfizer laboratories for analysis. The concentration of active sildenafil ranged from 0–200% of indicated strength, and only 10% of the samples contained an

Table 2 Analysis of phosphodiesterase-5 inhibitors (PDE-5i) purchased from the Internet

Pharmacy	Information sheet provided?	Counterfeit or authentic	Percent active ingredient
Pharmacy 1	No	Authentic	n/a
Pharmacy 2	No	Counterfeit	30
Pharmacy 3	No	Authentic	n/a
Pharmacy 4	No	Counterfeit	40
Pharmacy 5	No	Counterfeit	35
Pharmacy 6	No	Counterfeit	35
Pharmacy 7	No	Counterfeit	45
Pharmacy 8	No	Counterfeit	30
Pharmacy 9	No	Counterfeit	30
Pharmacy 10	No	Counterfeit	30
Pharmacy 11	No	Counterfeit	30
Pharmacy 12	No	Counterfeit	40
Pharmacy 13	No	Counterfeit	50
Pharmacy 14	No	Counterfeit	35
Pharmacy 15	Yes	Authentic	n/a
Pharmacy 16	Yes	Authentic	n/a
Pharmacy 17	No	Counterfeit	30
Pharmacy 18	No	Counterfeit	40
Pharmacy 19	No	Counterfeit	35
Pharmacy 20	No	Counterfeit	35
Pharmacy 21	No	Counterfeit	30

PDE-5i products purchased from Internet pharmacies rarely contain the stated amount of active ingredient (17).

active ingredient within 10% of what was advertised on the packaging (27). Similar results were found in an analysis of counterfeit ED drugs sold in Italy, Austria, and Canada (28). These problems are magnified in developing countries with less regulation. In Indonesia, 100% of “Viagra” sold by street peddlers, 56% purchased in “drug stores”, and 13% acquired from legitimate pharmacies was counterfeit Viagra marked as authentic (29). In pills marked as 100 mg, 64% contained <50 mg, 25.5% contained between 50–95 mg, and only 4.7% contained between 95 to 105 mg; 5.7% contained >105 mg (30). Quantities of active ingredients are also highly variable, as seen in *Table 2*. The effects of

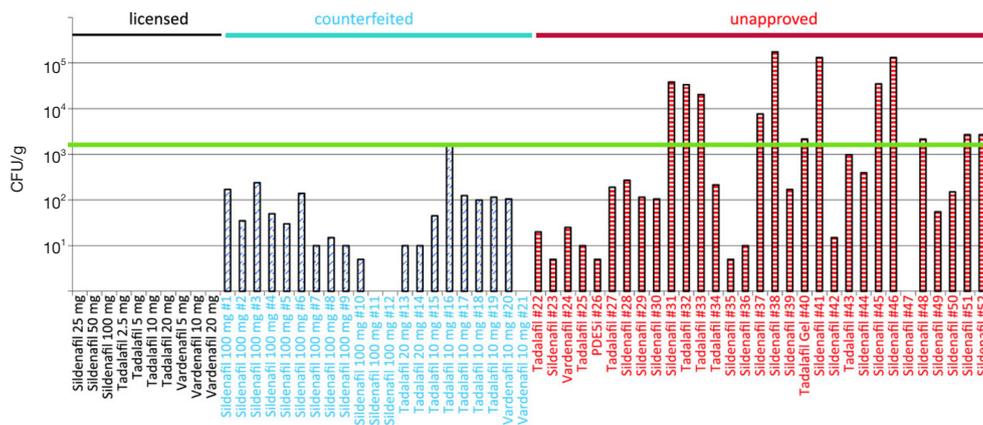


Figure 1 Microbial growth analysis of phosphodiesterase-5 inhibitors (PDE-5i) products (29).

widely variable amounts of active ingredient range from low efficacy at a minimum to severe side effects and negative drug interactions at the worst. As stated, counterfeit PDE-5i rarely are packaged with the appropriate warning labels.

In addition, counterfeit PDE-5i often contain contaminants. These are used either as bulking agents to lower production costs or to imitate the appearance and physical qualities of the genuine product. In those samples seized in the United Kingdom, Italy, and Indonesia, there were contaminants such as gypsum, non-purified talc, amphetamine, commercial grade paints, paracetamol, and metronidazole (27,28,30). These non-pharmaceutical ingredients can have toxicities of their own. Non-declared pharmaceuticals can have drug interactions and side effects such as gastrointestinal symptoms and nausea when combining metronidazole and alcohol. Counterfeiters do not declare these ingredients or warnings of possible deleterious interactions on their packaging.

Furthermore, the manufacturing conditions of counterfeiters cannot match the sterile processing conditions of legitimate pharmaceuticals. In an analysis of microbial loads of various illicit ED drugs, 23% were contaminated with more than 10^3 colony-forming units (CFU), and 69% had elevated levels considered within acceptable limits. Not a single CFU was detected in any of the approved PDE-5i obtained legally (29) (Figure 1). These results are not surprising, when considering the strict regulations and inspections that legitimate pharmaceutical producers must pass, compared with the unsterile conditions in which counterfeiters may work. Many laboratories of counterfeiters are exposed to the open air and use unsterile water that would not be safe for drinking. Contamination

with either adulterants or bacteria poses risks to consumers of counterfeit PDE-5i.

What about alternative ED medicines?

Perhaps even more dangerous than the counterfeit PDE-5i that is marketed as legitimate pharmaceuticals, however, are those marketed as “natural” supplements. Unlike pharmaceuticals requiring prescriptions, there is little Food and Drug Administration (FDA) regulation of health supplements. As a result, many so-called “natural” supplements, in fact, contain active ingredients of prescription strength drugs that could be potentially harmful. In a well-known example, 150 non-diabetic patients were hospitalized with hypoglycemia in Singapore. Seven patients fell into a comatose state, and four subsequently died. The common link between these patients was the use of an ED supplement that contained glyburide (a sulfonylurea used to treat diabetes), as well as illicit PDE-5i (31). In one study, the ingredients of 58 products available for the treatment of ED without a prescription were analyzed. Even though 57 of 58 products were labeled as “all natural” and no sample claimed to include synthetic substances, 81% contained PDE-5i. Several contained higher-than-approved amounts of PDE-5i, and others contained PDE-5i analogs that are not approved for use. One even contained phentolamine, an alpha-blocker, with which concurrent use with PDE-5i is contraindicated. Packaging and labeling were inadequate, and only 14 samples warned against concomitant nitrate use, a potentially fatal drug interaction (32). Recently, in January of 2016, the FDA announced warnings against 40 products

Table 3 Supplements warned against in FDA investigation (33)

Supplement	Undeclared PDE-5i contained
Apexx	Sildenafil
Diamond 3500	Sildenafil and tadalafil
Eros Power Zone 1900	Desmethyl carbodenafil and dapoxetine
OrgaZen 3000	Tadalafil
OrgaZen 3500	Tadalafil
Rhino Big Horn 3000	Desmethyl carbodenafil and sildenafil
Rhino 7 Blue 9000	Tadalafil
Triple MiracleZen Plus 1,500 mg	Sildenafil, tadalafil, and dapoxetine
Triple MiracleZen Gold 1,750 mg	Sildenafil, tadalafil, and dapoxetine
Triple MiracleZen Extreme 1,750 mg	Sildenafil, tadalafil, and dapoxetine
Triple Power Zen Gold 2000	Sildenafil and tadalafil
Triple Power Zen Plus 2000	Sildenafil and tadalafil
X Again Platinum	Sildenafil, tadalafil, and dapoxetine
Xtra Zone 2200	Sildenafil and tadalafil
Xtra Zone 2400	Sildenafil and tadalafil
Xtra Zone 2600	Sildenafil and tadalafil
Black Ant	Sildenafil
Herb Viagra	Sildenafil
Real Skill	Sildenafil
Stree Overlord	Sildenafil
Weekend Prince	Sildenafil
African Black Ant	Sildenafil
Bull	Unspecified
Bulls Genital	Unspecified
Zhonghua Niu Bian	Unspecified
African Superman	Unspecified
Bigger Longer More Time More Sperms	Unspecified
Black Ant King	Unspecified
Black Storm	Unspecified

Table 3 (continued)

Table 3 (continued)

Supplement	Undeclared PDE-5i contained
Germany Niubian	Unspecified
Happy Passengers	Unspecified
Plant Viagra	Unspecified
Hard Ten Days	Unspecified
Man King	Unspecified
Mojo Risen	Unspecified
Night Man	Unspecified
Tiger King	Unspecified
Samurai-X	Unspecified
Super Hard	Unspecified
Zhen Gong	Unspecified

marketed as dietary supplements that contained undeclared PDE-5i (33) (Table 3). Unsuspecting patients often seek alternative treatments of ED due to embarrassment and lower cost, but also because of the perception that “all natural” products are somehow safer than synthetic medications. However, by doing so, many of these patients are unknowingly subjecting themselves to significant health dangers.

What is being done to limit counterfeiting?

Strategies to limit counterfeiting should be multifaceted and target prescribing healthcare professionals, pharmaceutical companies, regulatory authorities, and patients. As such, in 2006, the WHO created a global coalition of stakeholders called International Medical Products Anti-Counterfeiting Taskforce (IMPACT), which aims to build coordinated networks across and between countries in order to halt the production, trading, and selling of fake medicines around the globe (34). Similarly, PDE-5i manufacturers have started working with regulatory and law enforcement authorities, as well as providing distinctive packaging using holographic security foil, 2D barcodes, and radio frequency identification (RFID) tags. The problem with RFID is the unfunded cost of implementation that has been estimated to range from \$84,000 for individual pharmacies to \$1.3 billion for large-chain pharmacies and may present significant barriers to

RFID adoption (35).

Similarly, the FDA has launched significant public education campaigns through magazine public service announcements, education leaflets, news articles, a consumer website (www.fda.gov/counterfeit), and a pharmacist education program (36).

Finally, it is the healthcare provider's responsibility to continue to support efforts to maintain consumer access to potency drugs, educate patients on the risks of counterfeit and other non-FDA approved products, remind them to only purchase from a VIPPS-certified pharmacy if they want to fill their prescription online, and report any suspected cases of counterfeit medicines to the FDA (37).

Conclusions

Counterfeit PDE-5i pose many—possibly serious—risks to patients. As the population ages, and the market for PDE-5i grow, so does the illicit market for PDE-5i. Counterfeit PDE-5i have become a worldwide problem that comprises a large percentage of PDE-5i use in both developing and well-developed countries. Patients embarrassed by their condition or seeking less expensive alternatives to legitimate pharmaceuticals have fueled the market, and the growth of Internet pharmaceuticals have made counterfeit pharmaceuticals easy to obtain. However, ED is a medical condition that needs to be treated as such. By bypassing the legitimate healthcare system, users of counterfeit PDE-5i bypass screening for concurrent medical comorbidities, as well as proper education and warnings of PDE-5i use. Furthermore, counterfeit PDE-5i often contain improper dosing and contaminants that may place patients at direct risk. Many “natural supplements” contain illicit PDE-5i, subjecting users to the same risks with even less warning. Physicians who treat ED should warn patients against purchasing PDE-5i via alternative means, especially the Internet. The use of dietary supplements for treatment of ED should be screened for and given due precautions.

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Footnote

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