Facing Counterfeit Medications in Sexual Medicine. A Systematic Scoping Review on Social Strategies and Technological Solutions

Andrea Sansone, MD, PhD,[1] Béatrice Cuzin, MD,[2] and Emmanuele A. Jannini, MD[1]

ABSTRACT

Introduction: The counterfeit phenomenon is a largely under-reported issue, with potentially large burden for healthcare. The market for counterfeit drugs used in sexual medicine, most notably type 5 phosphodiesterase inhibitors (PDE5i), is rapidly growing.

Aims: To report the health risks associated with the use of counterfeit medications, the reasons driving their use, and the strategies enacted to contain this phenomenon.

Methods: A systematic scoping review of the literature regarding counterfeit PDE5i was carried between January and June 2021, then updated in August 2021.

Main Outcome Measure: We primarily aimed to clarify the main drivers for counterfeit PDE5i use, the health risks associated, and the currently available strategies to fight counterfeiters.

Results: One hundred thirty-one records were considered for the present scoping review. Production of fake PDE5i is highly lucrative and the lacking awareness of the potential health risks makes it a largely exploitable market by counterfeiters. Adulteration with other drugs, microbial contamination and unreliable dosages make counterfeit medications a cause of worry also outside of the sexual medicine scope. Several laboratory techniques have been devised to identify and quantify the presence of other compounds in counterfeit medications. Strategies aimed at improving awareness, providing antitampering packaging and producing non-falsifiable products, such as the orodispersible formulations, are also described.

Clinical implications: Improving our understanding of the PDE5i counterfeit phenomenon can be helpful to promote awareness of this issue and to improve patient care.

Strengths & Limitations: Despite the systematic approach, few clinical studies were retrieved, and data concerning the prevalence of counterfeit PDE5i use is not available on a global scale.

Conclusion: The counterfeit phenomenon is a steadily growing issue, with PDE5i being the most counterfeited medication with potentially large harmful effects on unaware consumers. **Sansone A, Cuzin B, and Jannini EA. Facing Counterfeit Medications in Sexual Medicine. A Systematic Scoping Review on Social Strategies and Technological Solutions. Sex Med 2021;9:100437.**

Key Words: Fake Drugs; Counterfeit; PDE5 Inhibitors; Erectile Dysfunction; Premature Ejaculation; Patient Education

INTRODUCTION

The efficacy of type 5 phosphodiesterase inhibitors (PDE5i) has been verified by countless studies, and indeed these drugs have been included as the first-line treatment for the management of erectile dysfunction (ED).[1] It is therefore unsurprising that the general population has heard about these drugs, including patients with a very limited awareness of their sexual health. However, the widespread knowledge of these drugs in media and social networks[2] has made them widely adopted lifestyle drugs,[3] thus drawing the attention of counterfeiters.

Received June 30, 2021. Accepted August 20, 2021.

[1]Chair of Endocrinology and Medical Sexology (ENDOSEX), Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy;

[2]Division of Urology and Transplantation, Edouard Herriot Hospital, Lyon, France

https://doi.org/10.1016/j.esxm.2021.100437

The exact meaning of "counterfeit medicine" has been disputed in the last decades. The definition proposed by the World Health Organization (WHO) in 2009, which defined such drugs as "deliberately and fraudulently mislabeled with respect to identity and/or source", was recently revised in 2017, with an added warning concerning the exact composition of the drug ("deliberately or fraudulently misrepresent their identity, composition or source").[4] The WHO also proposed the definition of "substandard" drugs for all those products that are authorized on a local basis but fail to meet quality standards for or specifications.[4] While theoretically these definitions could be helpful in the identification of products of dubious origin, they have not been universally accepted, and there seems to be no worldwide policy aimed to fight the ever-increasing phenomenon of counterfeiting. National regulatory agencies have seldom joined efforts on an international scale, and the consequences for counterfeiters are generally less severe than one would expect.[5–8] For practical purposes, counterfeit drugs are those without any active pharmaceutical ingredients (APIs), or with different dosages of the intended APIs, or with fake packaging. Such drugs often include other pharmaceutical products than those intended, possibly increasing the health risks of consumers.[9]

In this scenario, experts in sexual medicine and andrologists should not underestimate the phenomenon of counterfeit medications. Counterfeit drugs used to improve sexual function represent a growing issue for public health, and while several strategies have been developed to fight counterfeiters, the market is constantly increasing. In the present systematic scoping review, we aimed to provide a thorough overview of the extent of this problem, answering the following questions: why do patients choose to actively look for counterfeit products, rather than following the traditional complaint-diagnosis-therapy track? What are the risks associated with counterfeit medications, and particularly with counterfeit PDE5i? Which are the possible strategies to prevent these risky behaviors?

METHODS

We systematically reviewed all publications found on PubMed and Google Scholar using the following search string: *(pde5 or phosphodiesterase or sildenafil or tadalafil or vardenafil or avanafil) and (fake or counterfeit or falsified)*. The initial systematic search was performed between January and June 2021, and a subsequent update was performed in August 2021. Results were limited to full articles written in English and/or Italian, without any date limitation and with no additional inclusion or exclusion criteria. The search string was purposely vague in order to adequately perform a scoping review – that is, "to identify knowledge gaps, scope a body of literature, clarify concepts or to investigate research conduct".[10] References of included papers were also scanned looking for additional content which would have been otherwise missed by our search queries. We also searched among reports by Organizations and Regulatory Agencies, such as the Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO) in order to retrieve additional material concerning the topic of counterfeit medical products, including, but not limited to, PDE5i.

RESULTS

As shown in Figure 1, following removal of duplicate results, 202 unique record were thus found, among which 12 were not assessed due to language constraints, 18 had no full-text available (including 5 conference abstracts) and 5 were not research papers (one conference program, one application note, and three investigation reports). One hundred sixty-seven full texts were thus evaluated, and 36 papers were considered off-topic for the present study. The remaining 131 papers and book chapters were considered for the present scoping review: among these results, 96 investigated available techniques for the analysis of counterfeit medical products,[5,11–105] 6 were case reports[53,92,106–109] (two of which also provided information on chemical analysis of the counterfeit drug), 7 were editorials,[7,110–115] 22 were reviews or guidelines,[6,8,9,116–134] and 2 studies reported patterns of use of counterfeit drugs in two different countries, namely a retrospective study in Brazil[135] and a prospective study in Japan.[136] According to our results, we identified the following four main topics for research: worldwide prevalence of counterfeit products, including PDE5i; health risks associated with the use of counterfeit PDE5i and other pro-erectile medications; social and psychological reasons for the counterfeit PDE5i phenomenon; and strategies to fight counterfeiting in sexual medicine (Figure 2).

DISCUSSION

The Numbers of the Counterfeits in the World. Regional Differences

Drug counterfeiting has been a known phenomenon for many centuries, with reports of fake antimalarial drugs being sold since the 17th century.[9] The real extent of counterfeit drugs being presently produced and sold is impossible to ascertain,[112,115,117,124,125] and even countries with no reported findings of counterfeited products are virtually non-exempt from this issue. The most recent WHO Global Surveillance and Monitoring System (GSMS) report on substandard and falsified medical products[4] highlights several factors limiting the reporting of inadequate products, such as low detection levels, cultural reasons to refrain from reporting, and the already mentioned blurry definition of counterfeit products in several countries. As an example, no reports were addressed between 2013 and 2017 to the WHO GSMS by many countries, including Canada, Portugal, and Australia: however, this is not an indication of no counterfeit medications being illegally sold, but rather that no reports were escalated to the WHO, possibly being investigated and managed internally. Furthermore, as counterfeit products are generally produced abroad and sold through the internet,[125] reports are closer to a depiction of the international situation than to the

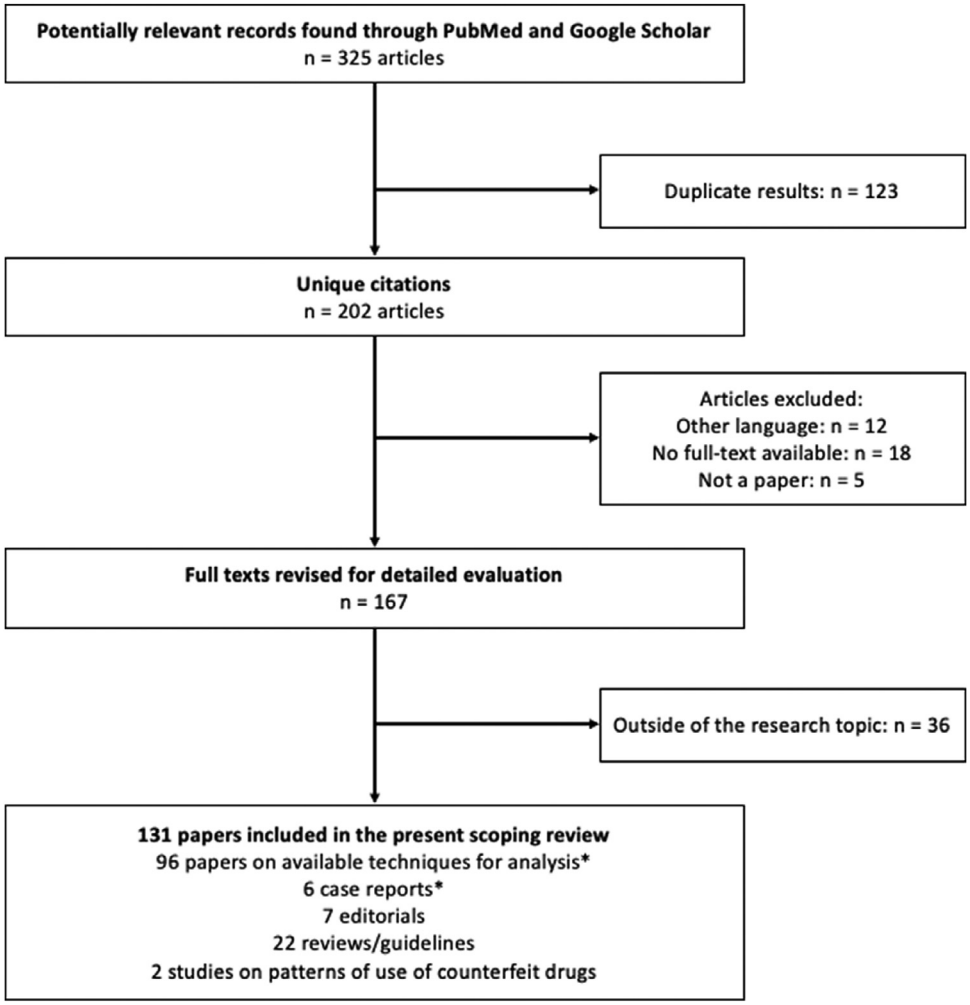

Figure 1. Flowchart of the papers included in the present systematic scoping review. *: two papers were included in both categories.

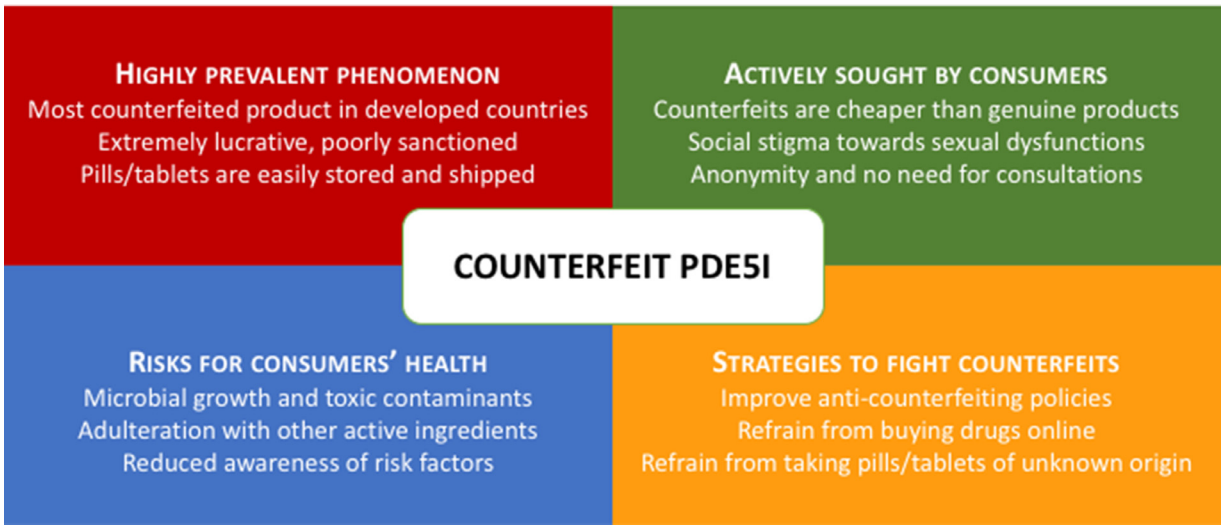

Figure 2. Counterfeit PDE5 inhibitors: pending issues.

snapshot of the reporting country.[65] It is also worth mentioning that in order to adequately address the issue of counterfeit medications, the involvement of several authorities (e.g. customs offices and police, but also healthcare professionals) actively searching for counterfeit products is necessary[114]: quoting the WHO GSMS, "The more one looks, the more one finds".[4]

The African region accounts for almost 42% of the reports addressed to the WHO GSMS between 2013 and 2017,[4] with antibiotics and antimalarials being the most counterfeited medical products, due to the high request in low-income, developing countries.[15,130,133] In many cases, individuals in poor economic conditions prefer to buy drugs at a cheaper price, despite being aware of the potential risks to their health, under the assumption that they would be better than the absence of any treatment whatsoever.[9] In some emerging countries, the prevalence of counterfeit drugs is estimated to be reaching up to 60%.[121]

Lifestyle drugs are the most counterfeited products found by police investigations in developed countries, such as in Europe and North America, with PDE5i having the largest share of the market and other appearance and performance enhancing drugs, such as anabolic androgen steroids, being close second.[65,73,125,126,135] For the largest part, the high prevalence of counterfeit PDE5i can be related to the well-known efficacy of these drugs, their supposed safety, and their commercial success.[45,126] Indeed, analysis of urban wastewater showed that in some European cities the concentration of sildenafil and its urinary metabolites was significantly higher than expected based on prescriptions, suggesting large illegal sources of drug acquisition.[70] While the FDA reports incidence of counterfeit drugs in the United States to be rare, relatively to the large number of prescription drugs used,[137] the amount of investigations due to drug fraud have been on the rise at least since 2000.[8] In Europe, almost 36 million counterfeited sildenafil tablets were sold between 2004 and 2008,[6] and in 2010 up to 2.5 million men were likely assuming "fake" sildenafil tablets, accounting for about 50% of its total use.[8] In Brazil, 80% of reports in regards to counterfeit drugs between 2007 and 2010 included counterfeit sildenafil or tadalafil[135]; in Japan, where men with ED can legally buy medications from abroad for private use, the online market for counterfeit PDE5i has grown exponentially, with reports from 2010 describing the market for counterfeits PDE5i being 2.5 larger than that of genuine PDE5i.[120,136] PDE5i are an extremely lucrative market for counterfeiters, as the revenue is estimated to be up to 2000 higher than that of cocaine while having much lower risks for the producers.[5–8,124]

The Risks of the Black Market for the Unaware User

The use of counterfeit medical products carries a significant risk for the user's health, due to several factors which are not always immediately obvious to the consumers themselves.

First and foremost, the largest health threats come from the use of wrong dosages of the intended drug – either too low to be effective, or at excessively high and possibly toxic levels, with large variations in drug contents.[6,59,67,125,129] The risk of overdosage of the medication is also possible for products with low content of the API, as consumers might be taking more than one tablet to achieve the desired effect.[6,18] However, in order to generate revenue and refrain the buyer to search for more efficacious products, counterfeiters are generally likely to use include the main API or similar active ingredients, or, as reported below, to add other APIs aiming to increase the efficacy.[7]

Counterfeit products are often produced in poor quality laboratories, resulting in the presence of residual solvents and contaminants in the finished product.[6,45,62,125,128,129] An analysis of counterfeited or illegal PDE5i collected between 2005 and 2011 in Italy reported that excipients were different than expected from a genuine product in 80% of analyzed samples, with presence of potentially toxic compounds in 17% of tablets.[19] These substances include ethanol, acetone, tetrachloromethane and dichloromethane[63] as well as paints and printer inks,[8] potentially harmful to the consumers as well as to the environment. Salts and compounds used during the preparation of the drugs can alter the pharmacodynamic properties of the main API,[91] and in some cases can act as APIs on their own, as reported for 2-Mercaptobenzothiazole-contaminated sildenafil tablets.[26]

Another potential risk comes from the use of different APIs in the preparation of the counterfeited product, either voluntarily, in order to increase efficacy,[59] or involuntarily, following inadequate quality control. For treatments used in sexual medicine, agents voluntarily added to increase efficacy include different drugs belonging to the same family (eg, vardenafil being added to sildenafil tablets[40]), or drugs potentially "synergistic" to the main product (eg, sildenafil being added to dapoxetine tablets[57]). While in theory the effects of the combined drugs might lead to increased efficacy, the risk of developing side effects is similarly increased; additionally, the association of these drugs is not recommended by any of the regulatory agencies or guidelines.[117,138-142] PDE5i can also be added to "sexual enhancement" herbal remedies in order to increase the efficacy of the products[6,30,47,76,79,116,118]: as an example, a herbal remedy sold as a "sexual enhancer" was found out to contain sildenafil and tadalafil in dosages up to 200 times the suggested dose.[106] Such high dosages, together with the presence of toxic solvents, are possibly leading to harmful effects for the unsuspecting user: indeed, acute liver injury and ischemic stroke have been reported following the intake of herbal remedies contaminated by sildenafil and/or tadalafil.[108,122,128] Likewise, analogues of PDE5i have been added to "functional foods" (eg, pseudovardenafil and hydroxyvardenafil in dietary supplements[79]) and counterfeit medications (eg, hongdenafil, homosildenafil and hydroxyhomosildenafil in counterfeit sildenafil[82]) to enhance the effects: safety and efficacy profiles of such substances have not been adequately investigated, possibly resulting in hazardous effects for the unaware user. Similar considerations can be made for dietary supplements sold with the claim to improve sexual health, whose adulteration can pose a risk to consumers' health.[23,128] On the other hand, adulteration with other APIs not intended to be

included in the product has the potential to generate unwanted side effects according to the contaminating drug. A clear picture of the potential risks associated with the use of contaminated drugs comes from an outbreak of hypoglycemia occurring in 2008 in Singapore: 150 nondiabetic men were admitted to public hospitals for hypoglycemia due to adulteration of both counterfeit tadalafil tablets and herbal remedies with glibenclamide, with lethal outcome for four of the involved consumers.[143] Following this first episode, several other occurrences of contamination with glibenclamide has been reported for both counterfeit PDE5i medications[53] and herbal remedies.[107,109] Adulteration of PDE5i with paracetamol or metronidazole[8] has similarly been reported. This phenomenon is not limited to drugs or remedies being taken to improve male sexual health: contamination of slimming products, skin creams, and analgesics[38] has also been reported, with orlistat, sibutramine, corticosteroids, and other appearance and performance enhancing drugs being added without being declared. Herbal supplements containing flibanserin and tadalafil have also been identified.[75] In some cases, the adulteration is seemingly accidental and a consequence of inappropriate laboratory procedures, as occurring with glibenclamide, although in many situations the inclusion of another API is voluntarily performed to enhance the efficacy of the treatment. Given that most, if not all, classes of medication are able to exert a tangible effect on sexual health − antidepressants, antihypertensives and opioids being known examples of this phenomenon − the issue of drug adulteration is extremely relevant for sexual medicine specialists.[6,113,115]

Microbial growth resulting from production of the counterfeited drug in nonsterile laboratories has also been reported.[69] Several bacteria able to cause infection, among which the most common were from the *Bacillus* genus, were identified: on the other hand, genuine products do not show signs of contamination.[69] This difference is hardly surprising, giving the strict good manufacturing practices required by regulatory agencies for the authorization and licensing of medical products and the generally poor hygienic conditions of clandestine laboratories.[6,9,65,69]

Health Risks of Unsupervised Use of Counterfeit PDE5i

Another issue, largely unrecognized by most subjects buying counterfeit products online, lies in the unsupervised use of the intended API. Concerning treatments for sexual dysfunctions, while PDE5i have a generally good safety profile, clinicians prescribing these drugs should be well aware of the potential contraindications in selected patients, such as those undergoing nitrate therapies: individuals buying these drugs online might not be aware of the potential risks associated with other concomitant treatments.[112,115] Cases of sexual activity related deaths have also been reported due to nonprescription use of PDE5i in high-risk patients, partly because of underlying conditions, and partly because of the use of combined use of multiple PDE5i.[144] Some websites only provide high dosages of PDE5i, without mentioning the suggested "starting" dose for any naïve patient.[57] Additionally, first-line treatments for ED include pursuing a healthier lifestyle, such as by limiting alcohol intake, reducing harm from tobacco smoking and performing physical exercise[112,145,146]: individuals buying "sexual enhancers" online, or getting them from friends without any prior clinical evaluation, are generally less aware of the pathophysiology of sexual dysfunctions[115] and thus less likely to investigate for any underlying condition, such as endocrine dysfunctions including hypogonadism[147,148] and diabetes,[138,149,150] or metabolic and cardiovascular diseases,[150−152] possibly resulting in ED.[136,153] The unsupervised use of PDE5i might therefore reduce the rate of diagnosis for ED-associated diseases.[8,115,154] Worryingly, this phenomenon is not limited to drugs for sexual dysfunctions: indeed, several reports suggest that internet can be used in order to circumvent doctors' opinions and consultations also concerning other conditions.[7,8]

Another fundamental professional help is skipped when buying online counterfeit PED5is, that is, that one from the pharmacist.[123] The selling of sildenafil out of the counter in countries as United Kingdom and Norway ensured a higher degree of accuracy and specificity in the patient and pharmacist decision-making around suitability for use.[155] Moreover, it could be inferred that the peculiar pharmacist-client relationship may result in a more "horizontal" than "vertical" information which is to be *bona fide* considered particularly efficient when complex therapeutical strategies, such as changes in lifestyle, have to be prescribed.[123] However, a recent online survey on 668 Italian pharmacists demonstrated that they have limited knowledge about falsified drugs in general, with only 24.5% of respondents failing to indicate that falsified drugs may contain less or different ingredients, 46.4% less and/or different excipients, and 72.3% ignoring that falsified drugs may be lethal.[156] One in 3 respondents did not know about falsified drugs in Italy. These findings demonstrated that, without targeted, continuous and strong educational interventions the pharmacists' community could be hardly considered a resource against the risk of counterfeits in the field of ED treatment.[123] The need of specific education of the pharmacist in identifying falsified medicines has been found as a major strategy also in United Kingdom.[157]

Additionally, while buyers are often enticed by the possibility of getting the desired drug at a cheaper price, this is rarely the case, due to several "hidden" costs, including shipment, customs clearance, online medical consultations, additional packaging and so forth[112]; additionally, in the case that no products are received by the buyer, there is little, if any at all, chance to retrieve all money spent. This is, of course, on top of the potential risks associated with sharing payment information on "shady" websites, such as "phishing" and other forms of digital threats.

The Psychological and Social Reasons of the Phenomenon

From a distance, it would be easy to identify 2 categories of "victims" of counterfeit drugs: patients who receive a prescription from a healthcare specialist and look for cheaper alternatives to pharmacies and individuals who seek treatments without any prior consultation.[7] This generalization is fitting for all kinds of counterfeit medications, not being limited to drugs for sexual dysfunction only[7]: however, several factors contribute to the ever-growing market for falsified PDE5i.[112,121]

First and foremost, as previously reported, the high success of the genuine drugs made them quite recognized even to the general population and widely adopted worldwide.[116,121,129] ED is a frequent complaint in aging men,[158] and it is largely expected that many elderly people would look for treatment in order to improve their sexual health; however, there is compelling evidence that some individuals would take such drugs for recreational purposes in the absence of medical suggestion, even among younger men.[129,136,159-162] Considering the social stigma for ED, it is unsurprising that many subjects would prefer buying online, in full anonymity, rather than buying in person[18,65,117,129]: indeed, PDE5i have the highest prevalence among drugs bought through the internet,[8,125,129] and younger subjects are indeed those who buy drugs online more frequently.[112] Additionally, most fraudulent websites do not require prescriptions,[65] nor do they provide "remote" medical consultations.[8] The convenience of being able to buy the drugs at every time of the day and from mobile devices is another possible reason driving people towards online pharmacies or pseudo-pharmacies,[116] and in more recent days also toward other markets, such as social media.[2,113] Additionally, as the costs of these drugs are among the chief reasons for drop-out,[131,163] it is unsurprising that consumers might be looking for cheaper alternatives.

Herbal remedies are often promoted as "natural" supplements to improve sexual health, therefore giving to the unaware user the false perception of a safer and more reliable product with no side effects.[6,43,116,128] Once again, adulteration with PDE5i — performed in order to provide some effects, and hence generate repeat business[7] — makes the use of these products quite unsafe for consumers, who might develop severe side effects with little awareness of the medications they're involuntarily taking. Additionally, although several well conducted in vitro and in vivo studies demonstrated a role of herbal remedies in the management of male sexual health,[164–169] the potential effects of these remedies are largely disputed.[116]

While this is a relatively smaller phenomenon, some reports of counterfeit drugs being legally sold has been collected,[73,111] highlighting the potential of counterfeit products to reach the "regular" supply chain. It is, therefore, necessary to educate potential consumers in order to prevent them from falling prey to counterfeiters.

Compounded and Counterfeit Medications

It is not uncommon for patients to ask for compounded medications, that is, drugs prepared in a pharmacy laboratory by trained professionals; such products are clearly different from counterfeit medication, being the application of pharmaceutical expertise to provide tailored treatment. Historically, drug manufacture and preparation were among the chief tasks for a pharmacist in the past. As of today, the need for higher quality standards and for mass production has moved this process from pharmacies to industries; however, compounded medications are still prepared for tailored treatment of patients with particular needs. The FDA defines drug compounding as "the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient".[170] In Europe, the term "pharmacy preparation" is also used; European laws distinguish the 'magistral formula' ("any medicinal product prepared in a pharmacy following a prescription for an individual patient") from the 'officinal formula' ("any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia that is intended to be supplied directly to the patients served by the pharmacy").[171] Broadly speaking, compounded drugs are not as closely monitored as industrial products and do not follow good manufacturing practices, and are therefore not approved by Regulatory Agencies; however, as they fill a "niche" and can potentially allow or improve treatment in well-defined populations, pharmacy preparations can be used in selected settings.[171] Indeed, caution when using these drugs is necessary, as the use of pharmacy preparations has been associated to some of the risks reported for counterfeit medications, such as the presence of contaminants: in 2012, an outbreak of meningitis, with 64 deaths and 689 nonfatal complications[172] occurred following *Aspergillus fumigatus* contamination of methylprednisolone vials produced by the New England Compounding Center (NECC).[173] Likewise, compounded drugs might contain wrong dosages of the intended drug, possibly resulting in unreliable clinical effects. Despite these similarities, it is clear that counterfeit medications and compounded drugs are different products, with the former being produced by generally untrained individuals with no concerns for the users' health and the latter being instead carefully manufactured by trained professionals in order to address an unmet need.

The Costs of Counterfeit Medication for Society and Public Health

The use of counterfeit medication has several costs for society and public health,[127] from the damage to intellectual property to the already reported harmful effects to the consumer.

Damage to intellectual property — similarly to what occurring for software piracy or counterfeiting of non-medical products, such as toys, apparel or luxury goods — has hidden costs which are rarely clearly evident to the consumer,[127] such as the loss of revenue for the producer, the reduced availability of funds for research and development (R&D), and often loss of jobs for affected companies — "When Banks Fail, It Is Seldom Bankers Who Starve."[174] While this is true for all societies targeted by counterfeiters, it becomes of paramount importance for medical

companies, which spend large part of their revenue on R&D[127] and wouldn't find it profitable to engage in further research projects only to have them "stolen" by counterfeiters. As investments in R&D could be used to reduce prices of current products or to develop new drugs, a vicious cycle might develop in which request for cheaper, counterfeited products actually prevents companies from providing cheaper, effective products.

Harmful effects on consumers, on the other hand, might be more evident to the general population. First and foremost, money spent on a nonworking treatment is effectively lost, result in a direct economic damage to the user; the same would apply for unsuccessful transactions in which despite the payment, no product is received by the buyer.[127] The risks of unsupervised use of counterfeit drugs have already been described; additionally, use of tablets devoid of any active ingredients can have potentially serious consequences, as in the absence of any treatment, the underlying condition might progress, leading to worse clinical outcomes for the unaware user. On top of that, the public health costs of undesired effect of contaminants — whether microbial, chemical, or APIs — should also be considered: as occurred with the glibenclamide contamination,[143] use of counterfeited medication might also have potentially fatal consequences.[144] Liver damage, ischemic stroke, and kidney failure have been reported following accidental intake of toxic compounds or undeclared APIs: management of these conditions further weighs on public health.

Public Education: A Necessary Strategy in the Fight Against Counterfeiters

Based on current evidence, it can be assumed that the counterfeit market is flourishing because of an ever-increasing demand, largely supported by the lacking awareness of the health risks and sub-standard efficacy of these products.[133] As a consequence, strategies acting to reduce demand, mostly by raising awareness of the potential issues, could be a useful weapon in the fight against counterfeiters. Education thus becomes the most reliable way to prevent the spread of the counterfeit phenomenon, and physicians should always suggest their patients not to buy medications online.[117] Public education, however, is a daunting and complex challenge for public health, requiring the involvement of international authorities and the development of a shared policy to fight the counterfeit phenomenon. Indeed, in 2006, the WHO has launched the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), a network of experts aiming to halt the production and marketing of counterfeited medical products,[6] and likewise educational campaigns have been promoted in the United States[137] and in Europe.[175] The relevance of such multifaceted approaches has recently been rekindled by the illegal marketing of counterfeit COVID-19 vaccines,[176] highlighting the general disregard counterfeiters have for the health of patients. The EMA and the European Directorate for the Quality of Medicines (EDQM) are in first line in facing counterfeits and in studying strategies to reduce the epidemy of falsified medicinal products. Henceforth, the Council of Europe is currently supporting an international convention dealing with the criminal law field on counterfeiting of medical products and similar crimes involving threats to public health.[177] The States Parties must criminalize: (i) the manufacturing of counterfeit medical products; (ii) supplying, offering to supply and trafficking in counterfeit medical products; (iii) the falsification of documents; (iv) the unauthorized manufacturing or supplying of medicinal products and the placing on the market of medical devices which do not comply with conformity requirements. The chart of signatures and ratifications shows that, as of April 20, 2021, some Members did not sign nor ratify the document yet (Andorra, Azerbaijan, Bulgaria, Czech Republic, Estonia, Georgia, Greece, Ireland, Latvia, Malta, Monaco, Montenegro, Netherlands, North Macedonia, Norway, Poland, Romania, Slovak Republic, Sweden, and United Kingdom), but the largest European States did, as well others not members of the Council, such as Belarus, Benin, Burkina Faso, Côte d'Ivoire, Guinea, Israel, Marocco, and Niger.[178] These regional differences suggest that this strategy is not universally perceived as convenient or effective in facing counterfeits.

The FDA currently sponsors a public campaign named "BeSafeRx", characterized by a specific warning to beware of online pharmacies that: (i) allow to buy drugs without a prescription from the doctor; (ii) offer deep discounts or cheap prices that seem "too good to be true"; (iii) send spam or unsolicited e-mail offering cheap drugs; (iv) are located outside of the United States.[179] No data have been published yet on the efficacy of the campaign, but it is to be noted that this strategy addresses only indirectly the issue of the counterfeit drugs.

The Fakeshare is a European project coordinated by the Italian Medicines Agency (AIFA), launched in 2013 and aiming to produce public awareness on the pandemic use of counterfeit medicines in the continent. The project produced a public advertisement translated in the European languages showing the risks of these products, such as a picture of a male (not by chance) mouth with a gun bullet on the tongue ready to swallow illustrating the message "Buying Medicine online: Think you know what you are getting?".[180] Although meritorious, the output and the social redemption of this campaign are not known.

Machine Learning, which has been used with some successes to combat digital opioid access,[181] has also been considered among the possible strategies to face the increasing use of social networks, like Facebook, Instagram, and Twitter,[2,113] to spread and sell illegal and counterfeit drugs. However, this solution has not been adopted yet to detect, classify, and report illicit online marketing and sales of drugs for sexual medicine.

Additionally, the enactment of telemedicine during COVID-19 has proven that remote consultations are an attractive approach for sexual health, as for many other branches of clinical medicine.[182,183] While clinical assessment cannot be fully performed with a video interview, there is no doubt that a remote

consultation would be far more beneficial than "asking doctor Google".[184,185]

Telemedicine might also be beneficial in the fight against counterfeit medications: the availability of quick, anonymous and possibly cheap remote consultations issued by certified specialists might encourage patients to refrain from self-diagnosis and self-treatment. However, no definite evidence exists at this time of the efficacy of this strategy.

Technological Solutions Against Counterfeit Medications

While social interventions are fundamental to contrast counterfeit drugs, technical solutions may also be crucial and could be helpful to overcome the potential gaps (Figure 3). While, as a rule of thumb, it would be wise to refrain from buying drugs online at all, it is not uncommon for people to get PDE5i from peers such as friends and colleagues,[136] with little information, if any, on the source of the drug. Several studies performed in the last years have collected the telltale signs of a counterfeit medication: drugs shipped or sold without accompanying leaflets or outer packaging, missing a clear expiration date or information on manufacturing country[19,65] are most likely not genuine products. Since pills and tablets are the most likely products to be counterfeited and their form allows for easy storage (once again, increasing the risks of microbial contamination), the product's shape, color and aspect can be selected or modified by the manufacturer to increase similarity to the genuine product. Therefore, several strategies have also been envisioned by pharmaceutical companies to identify a counterfeit product by the external packaging only, including the use of serial numbers, barcodes, holography, radiofrequency identification device, or unreplaceable sealings on the package itself.[119] While theoretically able to solve the issue of counterfeit medications, such strategies are not always applicable: as an example, the costs for the radiofrequency identification device method are often excessively high, reaching up to billion dollars for large-chain pharmacies,[6,186] and serialization requires several checks by manufacturers, importers, distributors and resellers, with some countries unable to meet the deadline proposed by regulatory agencies. Of course, this is on top of other concerns, such as the issue of patients' privacy and data security.[7] This once again highlights the need of a more comprehensive approach, supported by larger authorities, such as FDA and WHO.

From a technical point of view, different analyses on samples are available to researchers having access to a modern laboratory[134]: several techniques have been successfully used in the last decades to perform assessment of any tablet's contents (Table 1). While some chromatography techniques require destruction of the tablet itself, possibly becoming a problem from a legal point of view,[14,68] nondestructive techniques, such as near-infrared spectroscopy,[14] Raman spectroscopy[12] or nuclear magnetic resonance relaxometry,[48,132] could be helpful in these regards by leaving the tablet intact. Available techniques also differ for sensitivity, costs, required training and personnel, limiting the possible applications in different settings: therefore, relying upon technical investigations alone in order to identify all counterfeit medications being shipped worldwide is not a feasible strategy.

Last, but not least, among the possible pharmaceutical forms of the PDE5i, the orodispersible one seems particularly interesting for its pharmacokinetic characteristics.[187] In particular, the sildenafil orodispersible film (SODF), based on hydrophilic polymers with drug and other excipients, expresses the unique and peculiar ability to preserve the male intimacy through a convenient and discrete dosage form.[188] Differently from the other pharmaceutical formulations of the products belonging from the same class of drugs, being not easily recognized as a drug, the

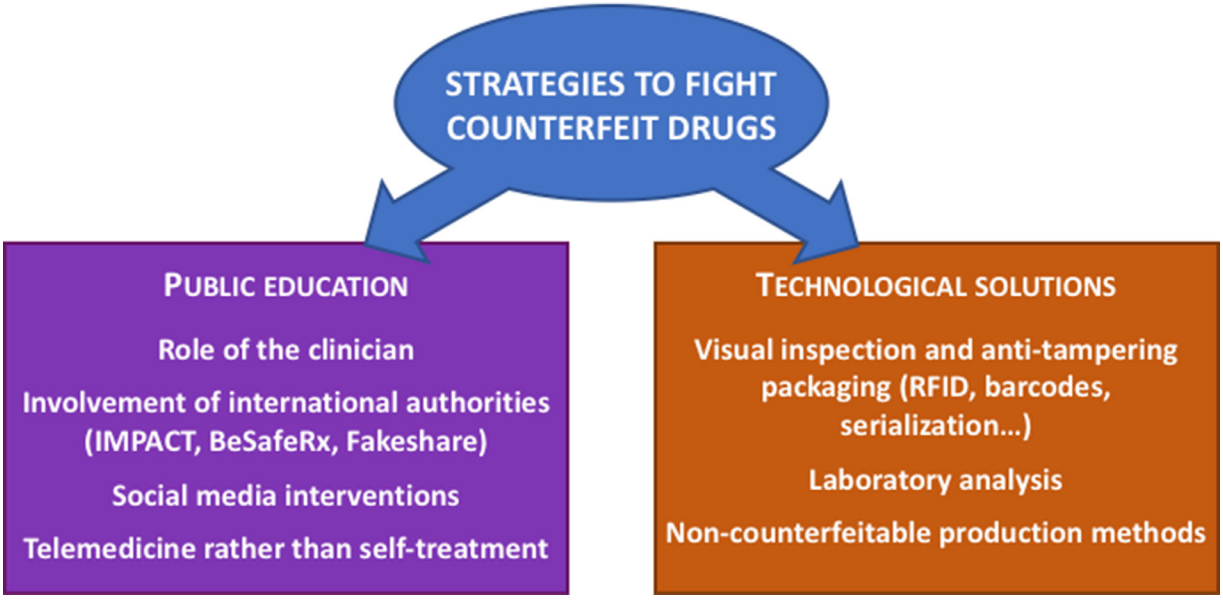

Figure 3. Strategies to fight counterfeit medications.

Table 1. Methods used to investigate quality of counterfeit PDE5i and/or prevalence of contaminants

Method used	Reference(s)
Atmospheric solids analysis probe with time-of-flight mass spectrometry (ASAP-TOF-MS)	47
Attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy	26,44–46,103,104
Calorimetry	88
Capillary electrophoresis	94
Chemometry	33
Chiroptical and vibrational spectroscopy	67
Chromatography	5,77
Desorption electrospray ionization (DESI) mass spectrometry	93
Differential scanning calorimetry (DSC)	19
Dissolution test	36,91
Dynamic thermal analysis	78
Fourier-transform infrared spectroscopy (FTIR)	14,19
Gas chromatography—mass spectrometry (GC-MS)	23,62–66,98
High performance anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD)—GC-MS	97
High-performance liquid chromatography (HPLC)	53–56
HPLC - mass spectrometry (HPLC-MS)	85,86
HPLC - tandem mass spectrometry (HPLC-MS/MS)	57,144
HPLC - diode array detector (HPLC-DAD)	26
HPLC - diode array detector - quadrupole-time-of-flight mass analyzer (HPLC-DAD-QTOF-MS)	43
HPLC - photo diode array (HPLC-PDA)	15,85-87
HPLC - quadrupole-time-of-flight mass analyzer (HPLC-QTOF)	76
HPLC - ultraviolet detection (HPLC-UV)	58-61,102
HPLC - charged aerosol detector (HPLC-CAD)	84
High-performance thin layer chromatography (HP-TLC)	83
Hyperspectral imaging techniques	96
Infrared spectroscopy (IR)	14,18,25,55,90
Instrumental neutron activation analysis (INAA)	41,42
Ion beam analysis (IBA)	42
Laser desorption/Ionization	89
Liquid chromatography (LC)	89
LC - quadrupole-time of flight mass spectrometry (LC-QTOF-MS)	82
LC - quadrupole-time of flight tandem mass spectrometry (LC-QTOF-MS/MS)	38,79–82
LC - charged aerosol detector (LC-CAD)	75
LC - diode array detector (LC-DAD)	75
LC - diode array detector and mass spectrometry (LC-DAD-MS)	49
LC - diode array detector and tandem mass spectrometry (LC-DAD-MS/MS)	50
LC - mass spectrometry (LC-MS)	18,33,41,65,73–75
LC - tandem mass spectrometry (LC-MS/MS)	66,70-72,101
Mass spectrometry (MS)	15
Melting	26
Microbial analysis	69
Microtomography	68
Multicollector inductively coupled plasma mass spectrometry (MC-ICPMS)	52
Near infrared (NIR) spectroscopy	14,35,36,49–51
Nuclear magnetic resonance (RMN) relaxometry	48
Nuclear magnetic resonance (RMN) spectroscopy	13,26,33,37–40
Paper spray ionization (PSI) — Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR MS)	105
Physical profiling	25,103
Raman spectroscopy	12–14,17,18,20,26-28,34–36
Spectrophotometry	95
Tandem mass spectrometry (MS/MS)	24
Thermo-gravimetry (TG)	19

(continued)

Table 1. Continued

Method used	Reference(s)
Ultra-performance liquid chromatography (U-HPLC)	32,100
Ultra-performance liquid chromatography - high resolution tandem mass spectrometry (U-HPLC–HRMS/MS)	29,30
Ultra-performance liquid chromatography - mass spectrometry (U-HPLC-MS)	22
Ultra-performance liquid chromatography - ultra violet detection (UHPLC-UV)	16
Ultra-performance liquid chromatography hybrid-ion trap-Orbitrap mass spectrometry (UHPLC-Orbitrap-MS/MS)	26
Ultra-performance liquid chromatography quadrupole-time of flight tandem mass spectrometry (UPLC-QTOF-MS/MS)	26
Ultra-performance liquid chromatography-time-of-flight mass spectrometry (UHPLC/Q-TOF-MS)	23
Ultraviolet spectroscopy	18
Ultraviolet−visible spectroscopy (UV-VIS)	33
Visual inspection	19
Volume holograms	99
X-ray diffractometry	11,15
X-ray fluorescence (XRF) spectrometry	21,31

SODF could be classified as an "intimacy-sparing" PDE5i. Moreover, SODF does not require the intake of a liquid, hence reducing the anxiety of the patient and the stigma of assuming a well recognizable drug to address ED, while the large surface area leads to rapid disintegration in the mouth.[188]

A very interesting add on is the fact that the SODF appear as the unique PDE5i virtually exempt from the risk of counterfeiting.[189,190] On top of the still valid patents for ODF,[191,192] production of such formulations require, in fact, several expensive steps needing highly specialized laboratories and materials[131] (ie, IBSA ODF): as an example, the hygroscopic nature of the support and of the drug require special precautions during production, and excessively long exposure before individual packaging could damage the quality and efficacy of the drug.[189] In fact, the performance of SODF is dependent on manufacturing processes that maximize the porous structure of the tablet matrix, incorporating a disintegrating agent, and the use of highly water-soluble excipients to allow quick ingress of water, finally facilitating rapid oral disintegration[193]; all technical aspects which are tremendously hard to be replicated in the black-market setting. Therefore, on top of the already demonstrated safety and efficacy,[187,194−196] the reliability and reduced risk of counterfeiting are additional added benefits of the SODF formulation.

Strengths and Limitations

In this review, we systematically reviewed currently available literature concerning the use of counterfeit PDE5i, highlighting several topics relevant for sexual medicine experts as well as for the general population. To our best knowledge, this is the first time that this topic has been addressed systematically, highlighting all known risks for individual and public health as well as pointing out available strategies aimed to contain the counterfeit phenomenon, and reasons for their partial success. The present paper, however, has some limitations, mostly inherent to the available literature being investigated − such as the lack of any clear rate of counterfeit medication use and the presence of a limited amount of clinical studies.

CONCLUSION

While generally under-reported, counterfeit medications are a tangible issue requiring intervention, due to the potential risks for healthcare. This becomes of paramount importance in the context of sexual medicine, being pro-erectile drugs the most counterfeited products in several countries. As reported in different guidelines,[117,138−142] PDE5i are safe and effective if appropriately used; however, several risks and complications might arise following use of counterfeit medications. Microbial contamination, inadequate dosing of the active pharmaceutical ingredients and adulteration with other drugs or toxic compounds can both have direct effects on the consumers' health; additionally, unsupervised use results in decreased awareness of the underlying risk factors, increasing the potential burden for healthcare. Such costs should also consider the reduced reinvestments on R&D by medical companies, as well as the potential costs for public health from inadequate treatment and side effects of contaminants. While technologies to detect counterfeit are increasingly available, political aspects and the costs and required expertise limit their application. Within the various pharmaceutical formulations, the ODF is the less likely to be prone to be counterfeited and warrants a unique originality of its content, dosage, and safety. Physicians treating sexual dysfunctions and pharmacists should inform their patients and clients about the issues of counterfeit medical products, as well as suggest refraining from buying drugs online and taking tablets of dubious origin from peers.

Corresponding Author: Emmanuele A. Jannini, MD, Chair of Endocrinology and Medical Sexology (ENDOSEX),

Department of Systems Medicine, University of Rome Tor Vergata, Via Montpellier 1, 00133, Rome, Italy. Tel.: +390672596613; E-mail: eajannini@gmail.com

Conflict of Interest: EAJ has been speaker and or paid consultant for Bayer, Ibsa, Lundbeck, Menarini, Otsuka, Pfizer, Shionogi, and Viatris. The other authors have no conflict of interests to declare.

Funding: This review was funded by IBSA International (Lugano, Switzerland).

STATEMENT OF AUTHORSHIP

Andrea Sansone, Emmanuele A. Jannini: Conceptualization; Andrea Sansone, Emmanuele A. Jannini: Methodology; Andrea Sansone: Investigation; Andrea Sansone: Writing – Original Draft; Andrea Sansone,Béatrice Cuzin, Emmanuele A. Jannini: Writing – Review & Editing; Emmanuele A. Jannini: Funding Acquisition; Emmanuele A. Jannini: Resources; Emmanuele A. Jannini: Supervision.

REFERENCES

1. Yafi FA, Jenkins L, Albersen M, et al. Erectile dysfunction. **Nat Rev Dis Primers 2016;2:16003.**
2. Sansone A, Cignarelli A, Ciocca G, et al. The sentiment analysis of tweets as a new tool to measure public perception of male erectile and ejaculatory dysfunctions. **Sex Med 2019;7:464–471.**
3. Corona G, Maggi M, Jannini EA. EDEUS, a real-life study on the users of phosphodiesterase type 5 inhibitors: Prevalence, perceptions, and health care-seeking behavior among European men with a focus on 2nd-generation avanafil. **Sex Med 2018;6:15–23.**
4. World Health Organization. WHO global surveillance and monitoring system. 2017. Available at: https://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/. Accessed April 9, 2021.
5. Deconinck E, Sacre PY, Courselle P, et al. Chemometrics and chromatographic fingerprints to discriminate and classify counterfeit medicines containing PDE-5 inhibitors. **Talanta 2012;100:123–133.**
6. Chiang J, Yafi FA, Dorsey Jr. PJ, et al. The dangers of sexual enhancement supplements and counterfeit drugs to "treat" erectile dysfunction. **Transl Androl Urol 2017;6:12–19.**
7. Jack A. Counterfeit medicines. Bitter pills. **BMJ 2007;335:1120–1121.**
8. Jackson G, Arver S, Banks I, et al. Counterfeit phosphodiesterase type 5 inhibitors pose significant safety risks. **Int J Clin Pract 2010;64:497–504.**
9. Glass BD. Counterfeit drugs and medical devices in developing countries. **Res Rep Trop Med 2014;5:11–22.**
10. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. **BMC Med Res Methodol 2018;18:143.**
11. Maurin JK, Plucinski F, Mazurek AP, et al. The usefulness of simple X-ray powder diffraction analysis for counterfeit control—The viagra example. **J Pharm Biomed Anal 2007;43:1514–1518.**
12. de Veij M, Deneckere A, Vandenabeele P, et al. Detection of counterfeit viagra with Raman spectroscopy. **J Pharm Biomed Anal 2008;46:303–309.**
13. Trefi S, Routaboul C, Hamieh S, et al. Analysis of illegally manufactured formulations of tadalafil (Cialis) by 1H NMR, 2D DOSY 1H NMR and Raman spectroscopy. **J Pharm Biomed Anal 2008;47:103–113.**
14. Sacre PY, Deconinck E, De Beer T, et al. Comparison and combination of spectroscopic techniques for the detection of counterfeit medicines. **J Pharm Biomed Anal 2010;53:445–453.**
15. Newton PN, Green MD, Mildenhall DC, et al. Poor quality vital anti-malarials in Africa - An urgent neglected public health priority. **Malar J 2011;10:352.**
16. Sacre PY, Deconinck E, Chiap P, et al. Development and validation of a ultra-high-performance liquid chromatography-UV method for the detection and quantification of erectile dysfunction drugs and some of their analogues found in counterfeit medicines. **J Chromatogr A 2011;1218:6439–6447.**
17. Sacre PY, Deconinck E, Saerens L, et al. Detection of counterfeit Viagra(R) by Raman microspectroscopy imaging and multivariate analysis. **J Pharm Biomed Anal 2011;56:454–461.**
18. Campbell N, Clark JP, Stecher VJ, et al. Internet-ordered viagra (sildenafil citrate) is rarely genuine. **J Sex Med 2012;9:2943–2951.**
19. Gaudiano MC, Manna L, Rodomonte AL, et al. A survey on illegal and counterfeit medicines for the treatment of erectile dysfunctions in Italy. **J Sex Med 2012;9:2130–2137.**
20. Kwok K, Taylor LS. Analysis of counterfeit Cialis(R) tablets using Raman microscopy and multivariate curve resolution. **J Pharm Biomed Anal 2012;66:126–135.**
21. Ortiz RS, Mariotti KC, Schwab NV, et al. Fingerprinting of sildenafil citrate and tadalafil tablets in pharmaceutical formulations via X-ray fluorescence (XRF) spectrometry. **J Pharm Biomed Anal 2012;58:7–11.**
22. Ortiz RS, Mariotti Kde C, Holzschuh MH, et al. Profiling counterfeit cialis, viagra and analogs by UPLC-MS. **Forensic Sci Int 2013;229:13–20.**
23. Damiano F, Silva C, Gregori A, et al. Analysis of illicit dietary supplements sold in the Italian market: identification of a sildenafil thioderivative as adulterant using UPLC-TOF/MS and GC/MS. **Sci Justice 2014;54:228–237.**
24. Mustazza C, Borioni A, Rodomonte AL, et al. Characterization of Sildenafil analogs by MS/MS and NMR: A guidance for detection and structure elucidation of phosphodiesterase-5 inhibitors. **J Pharm Biomed Anal 2014;96:170–186.**
25. Custers D, Vandemoortele S, Bothy JL, et al. Physical profiling and IR spectroscopy: simple and effective methods to

discriminate between genuine and counterfeit samples of Viagra(R) and Cialis(R). **Drug Test Anal 2016;8:378–387.**

26. Keizers PHJ, Wiegard A, Venhuis BJ. The quality of sildenafil active substance of illegal source. **J Pharm Biomed Anal 2016;131:133–139.**
27. Lanzarotta A, Lorenz L, Batson JS, et al. Development and implementation of a pass/fail field-friendly method for detecting sildenafil in suspect pharmaceutical tablets using a handheld Raman spectrometer and silver colloids. **J Pharm Biomed Anal 2017;146:420–425.**
28. Rebiere H, Martin M, Ghyselinck C, et al. Raman chemical imaging for spectroscopic screening and direct quantification of falsified drugs. **J Pharm Biomed Anal 2018;148:316–323.**
29. Jiru M, Stranska-Zachariasova M, Dzuman Z, et al. Analysis of phosphodiesterase type 5 inhibitors as possible adulterants of botanical-based dietary supplements: Extensive survey of preparations available at the Czech market. **J Pharm Biomed Anal 2019;164:713–724.**
30. Lee JH, Park HN, Park S, et al. Development of a specific fragment pattern-based quadrupole-Orbitrap mass spectrometry method to screen adulterated products of phosphodiesterase-5 inhibitors and their analogues. **Sci Justice 2019;59:433–441.**
31. Soares F, Anzanello MJ, Fogliatto FS, et al. Enhancing counterfeit and illicit medicines grouping via feature selection and X-ray fluorescence spectrometry. **J Pharm Biomed Anal 2019;174:198–205.**
32. Benchekroun YH, El Karbane M, Ihssane B, et al. Application of design space, uncertainty, and risk profile strategies to the development and validation of UPLC method for the characterization of four authorized phosphodiesterase type 5 inhibitors to combat counterfeit drugs. **J AOAC Int 2020;103:715–724.**
33. Keizers PHJ, Bakker F, Ferreira J, et al. Benchtop NMR spectroscopy in the analysis of substandard and falsified medicines as well as illegal drugs. **J Pharm Biomed Anal 2020;178:112939.**
34. Sanada T, Yoshida N, Kimura K, et al. Discrimination of falsified erectile dysfunction medicines by use of an ultra-compact Raman scattering spectrometer. **Pharmacy (Basel) 2020;9:3.**
35. Sanada T, Yoshida N, Matsushita R, et al. Falsified tadalafil tablets distributed in Japan via the internet. **Forensic Sci Int 2020;307:110143.**
36. Zhu S, Yoshida N, Kimura K, et al. Falsified vardenafil tablets available online. **J Pharm Biomed Anal 2020;177:112872.**
37. Holzgrabe U, Malet-Martino M. Analytical challenges in drug counterfeiting and falsification-The NMR approach. **J Pharm Biomed Anal 2011;55:679–687.**
38. Johansson M, Fransson D, Rundlof T, et al. A general analytical platform and strategy in search for illegal drugs. **J Pharm Biomed Anal 2014;100:215–229.**
39. Ribeiro MVM, Boralle N, Felippe LG, et al. (1)H NMR determination of adulteration of anabolic steroids in seized drugs. **Steroids 2018;138:47–56.**
40. Trefi S, Gilard V, Balayssac S, et al. The usefulness of 2D DOSY and 3D DOSY-COSY 1H NMR for mixture analysis: Application to genuine and fake formulations of sildenafil (Viagra). **Magn Reson Chem 2009;47(Suppl 1):S163–S173.**
41. Romolo FS, Salvini A, Zelaschi F, et al. Instrumental neutron activation analysis (INAA) and liquid chromatography (LC) coupled to high resolution mass spectrometry (HRMS) characterisation of sildenafil based products seized on the Italian illegal market. **Forensic Sci Int 2019;1:126–136.**
42. Romolo FS, Sarilar M, Antoine J, et al. Ion beam analysis (IBA) and instrumental neutron activation analysis (INAA) for forensic characterisation of authentic Viagra(R) and of sildenafil-based illegal products. **Talanta 2021;224:121829.**
43. Bortolini C, Pivato A, Bogialli S, et al. "One-shot" analysis of PDE-5 inhibitors and analogues in counterfeit herbal natural products using an LC-DAD-QTOF system. **Anal Bioanal Chem 2015;407:6207–6216.**
44. Anzanello MJ, Yamashita G, Marcelo M, et al. A genetic algorithm-based framework for wavelength selection on sample categorization. **Drug Test Anal 2017;9:1172–1181.**
45. Coelho Neto J, Lisboa FLC. ATR-FTIR characterization of generic brand-named and counterfeit sildenafil- and tadalafil-based tablets found on the Brazilian market. **Sci Justice 2017;57:283–295.**
46. Kahmann A, Anzanello MJ, Fogliatto FS, et al. Interval importance index to select relevant ATR-FTIR wavenumber intervals for falsified drug classification. **J Pharm Biomed Anal 2018;158:494–503.**
47. Twohig M, Skilton SJ, Fujimoto G, et al. Rapid detection and identification of counterfeit and [corrected] adulterated products of synthetic phosphodiesterase type-5 inhibitors with an atmospheric solids analysis probe. **Drug Test Anal 2010;2:45–50.**
48. Wilczynki S, Petelenz M, Florek-Wojciechowska M, et al. Verification of the authenticity of drugs by means of NMR relaxometry-Viagra((R)) as an example. **J Pharm Biomed Anal 2017;135:199–205.**
49. Venhuis BJ, Zomer G, Vredenbregt MJ, et al. The identification of (-)-trans-tadalafil, tadalafil, and sildenafil in counterfeit Cialis and the optical purity of tadalafil stereoisomers. **J Pharm Biomed Anal 2010;51:723–727.**
50. Venhuis BJ, Zwaagstra ME, Keizers PH, et al. Dose-to-dose variations with single packages of counterfeit medicines and adulterated dietary supplements as a potential source of false negatives and inaccurate health risk assessments. **J Pharm Biomed Anal 2014;89:158–165.**
51. Vredenbregt MJ, Blok-Tip L, Hoogerbrugge R, et al. Screening suspected counterfeit Viagra and imitations of Viagra with near-infrared spectroscopy. **J Pharm Biomed Anal 2006;40:840–849.**
52. Clough R, Evans P, Catterick T, et al. Delta34S measurements of sulfur by multicollector inductively coupled plasma mass spectrometry. **Anal Chem 2006;78:6126–6132.**

53. Chaubey SK, Sangla KS, Suthaharan EN, et al. Severe hypoglycaemia associated with ingesting counterfeit medication. **Med J Aust 2010;192:716–717.**
54. Fidan AK, Bakirdere S. Simultaneous determination of sildenafil and tadalafil in legal drugs, illicit/counterfeit drugs, and wastewater samples by high-performance liquid chromatography. **J AOAC Int 2016;99:923–928.**
55. Taher A, Setiawati A. VICTORY project: A study of counterfeit PDE5 inhibitor (sildenafil) in Indonesia. **Acta Med Indones 2013;45:290–294.**
56. Tomic S, Milcic N, Sokolic M, et al. Identification of counterfeit medicines for erectile dysfunction from an illegal supply chain. **Arh Hig Rada Toksikol 2010;61:69–75.**
57. Dean J, Klep R, Aquilina JW. Counterfeit dapoxetine sold on the internet contains undisclosed sildenafil. **Int J Clin Pract 2010;64:1319–1322.**
58. Fejos I, Neumajer G, Beni S, et al. Qualitative and quantitative analysis of PDE-5 inhibitors in counterfeit medicines and dietary supplements by HPLC-UV using sildenafil as a sole reference. **J Pharm Biomed Anal 2014;98:327–333.**
59. Park M, Ahn S. Quantitative analysis of sildenafil and tadalafil in various fake drugs recently distributed in Korea. **J Forensic Sci 2012;57:1637–1640.**
60. Sacre PY, Deconinck E, Daszykowski M, et al. Impurity fingerprints for the identification of counterfeit medicines—A feasibility study. **Anal Chim Acta 2011;701:224–231.**
61. Yoshida N, Khan MH, Tabata H, et al. A cross-sectional investigation of the quality of selected medicines in Cambodia in 2010. **BMC Pharmacol Toxicol 2014;15:13.**
62. Custers D, Canfyn M, Courselle P, et al. Headspace-gas chromatographic fingerprints to discriminate and classify counterfeit medicines. **Talanta 2014;123:78–88.**
63. Deconinck E, Canfyn M, Sacre PY, et al. Evaluation of the residual solvent content of counterfeit tablets and capsules. **J Pharm Biomed Anal 2013;81-82:80–88.**
64. Lee W, Kim HJ, Lee ME, et al. Reliable screening and classification of phosphodiesterase type 5 inhibitors in dietary supplements using gas chromatography /mass spectrometry combined with specific common ions. **J Chromatogr A 2020;1623:461210.**
65. Odoardi S, Mestria S, Biosa G, et al. An overview on performance and image enhancing drugs (PIEDs) confiscated in Italy in the period 2017-2019. **Clin Toxicol (Phila) 2021;59:47–52.**
66. Thevis M, Schrader Y, Thomas A, et al. Analysis of confiscated black market drugs using chromatographic and mass spectrometric approaches. **J Anal Toxicol 2008;32:232–240.**
67. Kralik F, Jirmasek P, Kuchar M, et al. Chiroptical and vibrational spectroscopic study of genuine and counterfeit medicines containing tadalafil. **Chirality 2018;30:560–567.**
68. Wilczynski S, Koprowski R, Stolecka-Warzecha A, et al. The use of microtomographic imaging in the identification of counterfeit medicines. **Talanta 2019;195:870–875.**
69. Pullirsch D, Bellemare J, Hackl A, et al. Microbiological contamination in counterfeit and unapproved drugs. **BMC Pharmacol Toxicol 2014;15:34.**
70. Causanilles A, Rojas Cantillano D, Emke E, et al. Comparison of phosphodiesterase type V inhibitors use in eight European cities through analysis of urban wastewater. **Environ Int 2018;115:279–284.**
71. Lee JH, Park HN, Park OR, et al. Screening of illegal sexual enhancement supplements and counterfeit drugs sold in the online and offline markets between 2014 and 2017. **Forensic Sci Int 2019;298:10–19.**
72. Venhuis BJ, de Voogt P, Emke E, et al. Success of rogue online pharmacies: Sewage study of sildenafil in the Netherlands. **BMJ 2014;349:g4317.**
73. Deconinck E, Vanhee C, Keizers P, et al. The occurrence of non-anatomical therapeutic chemical-international nonproprietary name molecules in suspected illegal or illegally traded health products in Europe: A retrospective and prospective study. **Drug Test Anal 2021;13:833–840.**
74. Lebel P, Gagnon J, Furtos A, et al. A rapid, quantitative liquid chromatography-mass spectrometry screening method for 71 active and 11 natural erectile dysfunction ingredients present in potentially adulterated or counterfeit products. **J Chromatogr A 2014;1343:143–151.**
75. Poplawska M, Blazewicz A, Zolek P, et al. Determination of flibanserin and tadalafil in supplements for women sexual desire enhancement using high-performance liquid chromatography with tandem mass spectrometer, diode array detector and charged aerosol detector. **J Pharm Biomed Anal 2014;94:45–53.**
76. Campbell N, Clark JP, Stecher VJ, et al. Adulteration of purported herbal and natural sexual performance enhancement dietary supplements with synthetic phosphodiesterase type 5 inhibitors. **J Sex Med 2013;10:1842–1849.**
77. Krakowska B, Custers D, Deconinck E, et al. The Monte Carlo validation framework for the discriminant partial least squares model extended with variable selection methods applied to authenticity studies of Viagra(R) based on chromatographic impurity profiles. **Analyst 2016;141:1060–1070.**
78. Wilczynski S. The use of dynamic thermal analysis to distinguish between genuine and counterfeit drugs. **Int J Pharm 2015;490:16–21.**
79. Heo D, Kang JS, Choe S, et al. Metabolic study of vardenafil analogues: Pseudovardenafil and hydroxyvardenafil. **J Chromatogr B Analyt Technol Biomed Life Sci 2020;1139:121940.**
80. Lee S, Ji D, Park M, et al. Development of a comprehensive spectral library of sildenafil and related active analogues using LC-QTOF-MS and its application for screening counterfeit pharmaceuticals. **Forensic Sci Int 2015;257:182–188.**
81. Ozturk Er E, Ozbek B, Bakirdere S. Accurate and sensitive determination of sildenafil, tadalafil, vardenafil, and avanafil in illicit erectile dysfunction medications and human urine by LC with quadrupole-TOF-MS/MS and their behaviors in simulated gastric conditions. **J Sep Sci 2019;42:475–483.**

82. Yeo M, Park Y, Lee H, et al. New metabolites of hongdenafil, homosildenafil and hydroxyhomosildenafil. **J Pharm Biomed Anal 2018;149:586–590.**
83. Do TT, Theocharis G, Reich E. Simultaneous detection of three phosphodiesterase type 5 inhibitors and eight of their analogs in lifestyle products and screening for adulterants by high-performance thin-layer chromatography. **J AOAC Int 2015;98:1226–1233.**
84. Poplawska M, Blazewicz A, Bukowinska K, et al. Application of high-performance liquid chromatography with charged aerosol detection for universal quantitation of undeclared phosphodiesterase-5 inhibitors in herbal dietary supplements. **J Pharm Biomed Anal 2013;84:232–243.**
85. Custers D, Krakowska B, De Beer JO, et al. Testing of complementarity of PDA and MS detectors using chromatographic fingerprinting of genuine and counterfeit samples containing sildenafil citrate. **Anal Bioanal Chem 2016;408:1643–1656.**
86. Custers D, Krakowska B, De Beer JO, et al. Chromatographic impurity fingerprinting of genuine and counterfeit Cialis(R) as a means to compare the discriminating ability of PDA and MS detection. **Talanta 2016;146:540–548.**
87. Yoshida N, Yuasa M, Sovannarith T, et al. A cross-sectional investigation for verification of globalization of falsified medicines in Cambodia, indicated by tablets of sildenafil citrate. **Pharmacy (Basel) 2019;7.**
88. Dos Santos MK, de Cassia Mariotti K, Kahmann A, et al. Comparison between counterfeit and authentic medicines: A novel approach using differential scanning calorimetry and hierarchical cluster analysis. **J Pharm Biomed Anal 2019;166:304–309.**
89. Falco LFG, Melo C, de Oliveira DN, et al. An LDI-MSI approach for targeted and untargeted differentiation and assessment of pharmaceutical formulations. **Talanta 2019;197:92–97.**
90. Sabin GP, Lozano VA, Rocha WF, et al. Characterization of sildenafil citrate tablets of different sources by near infrared chemical imaging and chemometric tools. **J Pharm Biomed Anal 2013;85:207–212.**
91. Deconinck E, Andriessens S, Bothy JL, et al. Comparative dissolution study on counterfeit medicines of PDE-5 inhibitors. **J Pharm Anal 2014;4:250–257.**
92. Nagasawa S, Saka K, Yamagishi Y, et al. Association between sexual activity-related death and non-prescription use of phosphodiesterase type 5 inhibitors. **Leg Med (Tokyo) 2021;48:101815.**
93. Wiseman JM, Laughlin BC. Desorption electrospray ionization (DESI) mass spectrometry: A brief introduction and overview. **Curr Separat Drug Dev 2007;22:11–14.**
94. Rajh Vidal DT, Augelli MA, Lucio do Lago C. Determination of sildenafil and vardenafil by capillary zone electrophoresis using capacitively coupled contactless conductivity detection. **Anal Methods 2013;5:2041–2045.**
95. Azizi A, Tengah A, Petalcorin MIR. Developing a phosphodiesterase-5 inhibitor assay to detect counterfeit drugs containing phosphodiesterase-5 inhibitors using spectrophotometry. **F1000 Res 2019;8:1692.**
96. Coic L, Sacre PY, Dispas A, et al. Comparison of hyperspectral imaging techniques for the elucidation of falsified medicines composition. **Talanta 2019;198:457–463.**
97. Beasley E, Suman M, Coleman T. The use of high performance anion exchange chromatography for the detection of counterfeit pharmaceutical products using the excipient content as a marker. **Fields: J Huddersfield Student Res 2015;1:1.**
98. Ahmed A, Abdellah N, Shaltout E. Gas Chromatography-mass spectrometric analysis of a counterfeit sildenafil product and its potential hepatotoxicity in mice. **Mansoura J Forensic Med Clin Toxicol 2019;27:43–56.**
99. Meehl OJ. A first study on the suitability of volume holograms for use as integral security features on pharmaceuticals. Available at: http://rave.ohiolink.edu/etdc/view?acc_num=osu1593622852698023. Accessed August 6, 2021.
100. Reis NFA, Silva LFG, Souza M, et al. UHPLC for quality evaluation of genuine and illegal medicines containing sildenafil citrate and tadalafil. **J Chromatogr Sci 2021;59:30–39.**
101. Lee S, Choi B, Kim J, et al. An LC-MS/MS method for the determination of five erectile dysfunction drugs and their selected metabolites in hair. **J Chromatogr B Analyt Technol Biomed Life Sci 2015;978-979:1–10.**
102. Tero-Vescan A, Vari C, Filip C, et al. Analysis of dietary supplements and drugs for erectile dysfunction by HPLCUV. **Acta Med Transilvanica 2014;II:297–299.**
103. Coelho Neto J, Faraco RFP, Alves CF, et al. Genuine sildenafil tablets sold in Brazil disguised as MDMA. **Forensic Sci Int 2018;283:e8–e12.**
104. Pereira LSA, Lisboa FLC, Coelho Neto J, et al. Screening method for rapid classification of psychoactive substances in illicit tablets using mid infrared spectroscopy and PLS-DA. **Forensic Sci Int 2018;288:227–235.**
105. Kerpel dos Santos M, Araujo dos Santos N, Allochio Filho JF, et al. Paper spray ionization coupled to Fourier transform ion cyclotron resonance mass spectrometry as a tool to fight the counterfeiting of medicines. **Int J Mass Spectrom 2021;468:116649.**
106. Deliwala S, Haykal T, Dhillon H, et al. ST-elevation myocardial infarction and complete heart block in a nitrate-free patient using a new emerging substance called rhino. **Cureus 2020;12:e7601.**
107. Kuramoto N, Yabe D, Kurose T, et al. A case of hypoglycemia due to illegitimate sexual enhancement medication. **Diabetes Res Clin Pract 2015;108:e8–e10.**
108. Nissan R, Poperno A, Stein GY, et al. A case of hepatotoxicity induced by adulterated "Tiger King", a Chinese herbal medicine containing sildenafil. **Curr Drug Saf 2016;11:184–188.**
109. Ross JA, Downs JW, Bazydlo LA, et al. Outbreak of severe hypoglycemia after ingestion of a male enhancement supplement - Virginia, august-november 2019. **MMWR Morb Mortal Wkly Rep 2020;69:740–743.**

110. Dyer C. Internet supplier of fake Viagra is ordered to pay back 14.4m pound. **BMJ 2012;344:e3103.**
111. Gibson L. Counterfeits of impotence drug appear in the United Kingdom. **BMJ 2004;329:532.**
112. Hellstrom WJ. The growing concerns regarding counterfeit medications. **J Sex Med 2011;8:1–3.**
113. Liang BA, Mackey TK. Sexual medicine: Online risks to health—the problem of counterfeit drugs. **Nat Rev Urol 2012;9:480–482.**
114. The L. Combating counterfeit drugs. **Lancet 2008;371:1551.**
115. McMahon CG. Get a better erection!—Hope for sale—use sexual snake oil. **J Sex Med 2010;7:1699–1702.**
116. ElAmrawy F, ElAgouri G, Elnoweam O, et al. Adulterated and counterfeit male enhancement nutraceuticals and dietary supplements pose a real threat to the management of erectile dysfunction: A global perspective. **J Diet Suppl 2016;13:660–693.**
117. Hatzimouratidis K, Salonia A, Adaikan G, et al. Pharmacotherapy for erectile dysfunction: Recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). **J Sex Med 2016;13:465–488.**
118. Lowe G, Costabile R. Phosphodiesterase type 5 inhibitor abuse: a critical review. **Curr Drug Abuse Rev 2011;4:87–94.**
119. Shah RY, Prajapati PN, Agrawal YK. Anticounterfeit packaging technologies. **J Adv Pharm Technol Res 2010;1:368–373.**
120. Sugita M, Miyakawa M. Economic analysis of use of counterfeit drugs: health impairment risk of counterfeit phosphodiesterase type 5 inhibitor taken as an example. **Environ Health Prev Med 2010;15:244–251.**
121. Yafi FA, Sharlip ID, Becher EF. Update on the safety of phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. **Sex Med Rev 2018;6:242–252.**
122. Yelehe-Okouma M, Pape E, Humbertjean L, et al. Drug adulteration of sexual enhancement supplements: A worldwide insidious public health threat. **Fundam Clin Pharmacol 2021;35:792–807.**
123. Ziance RJ. Roles for pharmacy in combatting counterfeit drugs. ***J Am Pharm Assoc* (2003) 2008;48:e71–e88 quiz e89-91.**
124. Dorsey P, Keel C, Klavens M, et al. Phosphodiesterase type 5 (PDE5) inhibitors for the treatment of erectile dysfunction. **Expert Opin Pharmacother 2010;11:1109–1122.**
125. Jackson G, Patel S, Khan S. Assessing the problem of counterfeit medications in the United Kingdom. **Int J Clin Pract 2012;66:241–250.**
126. McVeigh J, Evans-Brown M, Bellis MA. Human enhancement drugs and the pursuit of perfection. **Adicciones 2012;24:185–190.**
127. Blackstone EA, Fuhr Jr. JP, Pociask S. The health and economic effects of counterfeit drugs. **Am Health Drug Benefits 2014;7:216–224.**
128. Israel J, Laborde EL. (2016) Alternative and internet drugs that affect sexual function. In: Köhler T, McVary K, editors. Contemporary treatment of erectile dysfunction. Contemporary Endocrinology. Humana Press, Cham. Available at: https://doi.org/10.1007/978-3-319-31587-4_10. Accessed August 6, 2021.
129. Capogrosso P, Ventimiglia E, Oreggia D, et al. Medical treatment of erectile dysfunction: Too many medical prescriptions? **Urologia 2017;84:121–129.**
130. Marlyna H, Sardjono A. Research report on the knowledge, experience, and attitude of consumers towards counterfeit medicine in Jakarta: A legal analysis. In: Harkrisnowo H, Juwana H, Oppusunggu Y, editors. Law and justice in a globalized world. London, UK: Taylor & Francis; 2018. p. 15–22.
131. Ouranidis A, Tsiaxerli A, Vardaka E, et al. Sildenafil 4.0-integrated synthetic chemistry, formulation and analytical strategies effecting immense therapeutic and societal impact in the fourth industrial era. **Pharmaceuticals (Basel) 2021;14:365.**
132. Santos ADC, Dutra LM, Menezes LRA, et al. Forensic NMR spectroscopy: Just a beginning of a promising partnership. **TrAC Trends Analyt Chem 2018;107:31–42.**
133. Nneka O, Olivia O. Investigation of consumers' knowledge about NAFDAC media campaign on consuming counterfeit drugs and substandard food in South East Nigeria. **IIARD Int J Econ Business Manag 2020;6:60–76.**
134. Singh S, Prasad B, Savaliya A, et al. Strategies for characterizing sildenafil, vardenafil, tadalafil and their analogues in herbal dietary supplements, and detecting counterfeit products containing these drugs. **TrAC Trends Analyt Chem 2009;28:13–28.**
135. Ames J, Souza DZ. Counterfeiting of drugs in Brazil. **Rev Saude Publica 2012;46:154–159.**
136. Kimura M, Shimura S, Kobayashi H, et al. Profiling characteristics of men who use phosphodiesterase type 5 inhibitors based on obtaining patterns: Data from the nationwide Japanese population. **J Sex Med 2012;9:1649–1658.**
137. U.S. Food and Drug Administration. Counterfeit medicine.
138. Mulhall JP, Giraldi A, Hackett G, et al. The 2018 revision to the process of Care Model for evaluation of erectile dysfunction. **J Sex Med 2018;15:1280–1292.**
139. Hackett G, Kirby M, Wylie K, et al. British Society for Sexual Medicine guidelines on the management of erectile dysfunction in men-2017. **J Sex Med 2018;15:430–457.**
140. Porst H, Burnett A, Brock G, et al. SOP conservative (medical and mechanical) treatment of erectile dysfunction. **J Sex Med 2013;10:130–171.**
141. Sansone A, Aversa A, Corona G, et al. Management of premature ejaculation: A clinical guideline from the Italian Society of Andrology and Sexual Medicine (SIAMS). **J Endocrinol Invest 2020;44:1103–1118.**
142. Salonia A, Bettocchi C, Boeri L, et al. European Association of Urology guidelines on sexual and reproductive health-2021 update: Male sexual dysfunction. **Eur Urol 2021;80:333–357.**
143. Kao SL, Chan CL, Tan B, et al. An unusual outbreak of hypoglycemia. **N Engl J Med 2009;360:734–736.**

144. Nagasawa S, Saka K, Yamagishi Y, et al. Association between sexual activity-related death and non-prescription use of phosphodiesterase type 5 inhibitors. **Leg Med 2021;48:101805.**

145. Corona G, Sansone A, Pallotti F, et al. People smoke for nicotine, but lose sexual and reproductive health for tar: A narrative review on the effect of cigarette smoking on male sexuality and reproduction. **J Endocrinol Invest 2020;43:1391–1408.**

146. Sansone A, Limoncin E, Colonnello E, et al. Harm reduction in sexual medicine. Sex Med Rev 2021. doi: 10.1016/j.sxmr.2021.01.005. E-pub ahead of print.

147. Sansone A, Romanelli F, Gianfrilli D, et al. Endocrine evaluation of erectile dysfunction. **Endocrine 2014;46:423–430.**

148. Sansone A, Kliesch S, Dugas M, et al. Serum concentrations of dihydrotestosterone are associated with symptoms of hypogonadism in biochemically eugonadal men. **J Endocrinol Invest. 2021**. doi: 10.1007/s40618-021-01561-0. E-pub ahead of print.

149. Sansone A, Mollaioli D, Ciocca G, et al. Sexual dysfunction in men and women with diabetes: A mirror of their complications? Curr Diabetes Rev. 2021. doi: 10.2174/1573399817666210309104740. E-pub ahead of print.

150. Jannini EA. SM = SM: The interface of systems medicine and sexual medicine for facing non-communicable diseases in a gender-dependent manner. **Sex Med Rev 2017;5:349–364.**

151. Sansone A, Cignarelli A, Sansone M, et al. Serum homocysteine levels in men with and without erectile dysfunction: A systematic review and meta-analysis. **Int J Endocrinol 2018;2018:7424792.**

152. Corona G, Rastrelli G, Monami M, et al. Frequency of sexual activity and cardiovascular risk in subjects with erectile dysfunction: Cross-sectional and longitudinal analyses. **Andrology 2013;1:864–871.**

153. Foresta C, Caretta N, Corona G, et al. Clinical and metabolic evaluation of subjects with erectile dysfunction: A review with a proposal flowchart. **Int J Androl 2009;32:198–211.**

154. Mollaioli D, Ciocca G, Limoncin E, et al. Lifestyles and sexuality in men and women: The gender perspective in sexual medicine. **Reprod Biol Endocrinol 2020;18:10.**

155. Symonds T, Dean JD, Carr A, et al. A feasibility study comparing pharmacist and physician recommendations for sildenafil treatment. **J Sex Med 2011;8:1463–1471.**

156. Lombardo S, Marino F, Cosentino M. A nationwide web-based survey of a sample of Italian community pharmacists' perceptions and opinions about online sales of medicines and falsified drugs. **Pharm Pract (Granada) 2019;17:1593.**

157. Barrett R. Evaluation of community pharmacists' readiness to implement the Falsified Medicines Directive (Directive 2011/62/EC): An English cross-sectional survey with geospatial analysis. **BMJ Open 2020;10:e033405.**

158. Romanelli F, Sansone A, Lenzi A. Erectile dysfunction in aging male. **Acta Biomed 2010;81(Suppl 1):89–94.**

159. Bechara A, Casabe A, De Bonis W, et al. Recreational use of phosphodiesterase type 5 inhibitors by healthy young men. **J Sex Med 2010;7:3736–3742.**

160. Korkes F, Costa-Matos A, Gasperini R, et al. Recreational use of PDE5 inhibitors by young healthy men: recognizing this issue among medical students. **J Sex Med 2008;5:2414–2418.**

161. Schnetzler G, Banks I, Kirby M, et al. Characteristics, behaviors, and attitudes of men bypassing the healthcare system when obtaining phosphodiesterase type 5 inhibitors. **J Sex Med 2010;7:1237–1246.**

162. Jannini EA, Sternbach N, Limoncin E, et al. Health-related characteristics and unmet needs of men with erectile dysfunction: A survey in five European countries. **J Sex Med 2014;11:40–50.**

163. Corona G, Rastrelli G, Burri A, et al. First-generation phosphodiesterase type 5 inhibitors dropout: a comprehensive review and meta-analysis. **Andrology 2016;4:1002–1009.**

164. Guo J, Wang F, Zhou Q, et al. Safety and efficacy of traditional Chinese medicine, Qiaoshao formula, combined with dapoxetine in the treatment of premature ejaculation: An open-label, real-life, retrospective multicentre study in Chinese men. **Andrologia 2021;53:e13915.**

165. Caggiano C, Guida E, Todaro F, et al. Sempervirine inhibits RNA polymerase I transcription independently from p53 in tumor cells. **Cell Death Discov 2020;6:111.**

166. Festuccia C, Mancini A, Gravina GL, et al. Antitumor effects of saffron-derived carotenoids in prostate cancer cell models. **Biomed Res Int 2014;2014:135048.**

167. Kamenov Z, Fileva S, Kalinov K, et al. Evaluation of the efficacy and safety of Tribulus terrestris in male sexual dysfunction—A prospective, randomized, double-blind, placebo-controlled clinical trial. **Maturitas 2017;99:20–26.**

168. Jannini EA, Lenzi A. Sexual dysfunction: Is acupuncture a therapeutic option for premature ejaculation? **Nat Rev Urol 2011;8:235–236.**

169. Virag R. Intracavernous injection of papaverine for erectile failure. **Lancet 1982;2:938.**

170. U.S. Food and Drug Administration. Compounding and the FDA: Questions and answers.

171. Minghetti P, Pantano D, Gennari CG, et al. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. **Health Policy 2014;117:328–333.**

172. Centers for Disease Control and Prevention. Multistate outbreak of fungal meningitis and other infections — Case count. Available at: https://www.cdc.gov/hai/outbreaks/meningitis.html. Accessed August 6, 2021.

173. Kauffman CA, Pappas PG, Patterson TF. Fungal infections associated with contaminated methylprednisolone injections. **N Engl J Med 2013;368:2495–2500.**

174. Pratchett T. Going postal. London, UK: Transworld; 2008.

175. European Commission. Falsified medicines. 2021. Available at: https://ec.europa.eu/health/human-use/falsified_medicines_en. Accessed August 6, 2021.

176. World Health Organization. Medical product alert N°2/2021: Falsified COVID-19 vaccine BNT162b2. 2021.
177. Venhuis BJ, Mosimann R, Wijnberg B. Medicrime convention: Against falsified medical products. **Lancet 2015;386:855–856.**
178. Council of Europe. Chart of signature and ratifications of treaty 211. 2021. Available at: https://www.coe.int/en/web/conventions/full-list?module=signatures-by-treaty&treaty-num=211. Accessed August 6, 2021.
179. U.S. Food and Drug Administration. BeSafeRx: Your source for online pharmacy information. 2020. Available at: https://www.fda.gov/drugs/quick-tips-buying-medicines-over-internet/besaferx-your-source-online-pharmacy-information. Accessed August 6, 2021.
180. Italian Medicines Agency. Fakeshare. 2020. Available at: http://www.fakeshare.eu/en/partners/aifa-italian-medicines-agency. Accessed August 6, 2021.
181. Mackey T, Kalyanam J, Klugman J, et al. Solution to detect, classify, and report illicit online marketing and sales of controlled substances via twitter: using machine learning and web forensics to combat digital opioid access. **J Med Internet Res 2018;20:e10029.**
182. Dooley AB, Houssaye N, Baum N. Use of telemedicine for sexual medicine patients. **Sex Med Rev 2020;8:507–517.**
183. Rabinowitz MJ, Kohn TP, Ellimoottil C, et al. The impact of telemedicine on sexual medicine at a Major Academic Center during the COVID-19 pandemic. **Sex Med 2021;9:100366.**
184. Russo GI, di Mauro M, Cocci A, et al. Consulting "Dr Google" for sexual dysfunction: A contemporary worldwide trend analysis. **Int J Impot Res 2020;32:455–461.**
185. Kirana PS, Gudeloglu A, Sansone A, et al. E-sexual health: A position statement of the European Society for Sexual Medicine. **J Sex Med 2020;17:1246–1253.**
186. Paxton M. Current challenges with supply-chain integrity and the threat to the quality of marketed drugs. **Clin Pharmacol Ther 2011;89:316–319.**
187. Scaglione F, Donde S, Hassan TA, et al. Phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction: Pharmacology and clinical impact of the sildenafil citrate orodispersible tablet formulation. **Clin Ther 2017;39:370–377.**
188. Jannini EA, Droupy S. Needs and expectations of patients with erectile dysfunction: An update on pharmacological innovations in phosphodiesterase type 5 inhibition with focus on sildenafil. **Sex Med 2019;7:1–10.**
189. Karki S, Kim H, Na S-J, et al. Thin films as an emerging platform for drug delivery. **Asian J Pharm Sci 2016;11:559–574.**
190. Trenfield SJ, Xian Tan H, Awad A, et al. Track-and-trace: Novel anti-counterfeit measures for 3D printed personalized drug products using smart material inks. **Int J Pharm 2019;567:118443.**
191. Borges AF, Silva C, Coelho JFJ, et al. Oral films: Current status and future perspectives. **J Control Release 2015;206:1–19.**
192. Borges AF, Silva C, Coelho JFJ, et al. Oral films: Current status and future perspectives II – Intellectual property, technologies and market needs. **J Control Release 2015;206:108–121.**
193. Goel H, Rai P, Rana V, et al. Orally disintegrating systems: Innovations in formulation and technology. **Recent Pat Drug Deliv Formul 2008;2:258–274.**
194. Cocci A, Capece M, Cito G, et al. Effectiveness and safety of oro-dispersible sildenafil in a new film formulation for the treatment of erectile dysfunction: Comparison between sildenafil 100-mg film-coated tablet and 75-mg oro-dispersible film. **J Sex Med 2017;14:1606–1611.**
195. Radicioni M, Castiglioni C, Giori A, et al. Bioequivalence study of a new sildenafil 100 mg orodispersible film compared to the conventional film-coated 100 mg tablet administered to healthy male volunteers. **Drug Des Devel Ther 2017;11:1183–1192.**
196. Isidori AM, Giammusso B, Corona G, et al. Diagnostic and therapeutic workup of erectile dysfunction: Results from a Delphi consensus of andrology experts. **Sex Med 2019;7:292–302.**