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Article *in* Harvard Health Policy Review · November 2014

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Digital Iatrogenesis: Policy Advocacy to Prevent Patient Harm from Access to Dangerous Drugs Online

By Tim K. Mackey, MAS, PhD,*&¶§ and Bryan A. Liang, MD, JD, PhD *¶§

Iatrogenesis is an old concept that has broadened in scope and depth since Ivan Illich's book Medical Nemesis sparked new debate about the need to recognize differences between clinical, social and cultural iatrogenesis types in the 1970s. Yet, in today's increasingly digitized world, there may be need for further modernization of iatrogenesis to reflect growing potential for patient harm from the Internet and related technologies. This specifically includes the patient safety and public health risks emanating from illicit online pharmacies, many of which sell questionable and counterfeit drugs directly to the patient. This piece outlines these risks, including summarized findings from studies showing that clearly dangerous drugs are available online. It also suggests a modernizing of iatrogenesis to include the new concept of "digital iatrogenesis" in order to raise awareness and address a constantly changing online health environment.

Iatrogenesis, or the "iatrogenic effect," is traditionally defined as preventable harm resulting from medical treatment or advice to a patient delivered by a health care professional. This is an ancient concept that has been recognized for centuries as early as the time of Hippocrates.[1] Effectively addressing underlining causes of iatrogenesis is a key component of the patient safety movement made prominent in the groundbreaking 1999 Institute of Medicine report "To Err is Human."[2,3]

Specifically, iatrogenesis can include adverse drug events caused by drug interactions, allergic reactions, and even treatment failure due to growing antibiotic drug resistance.[4,5] In addition, the concept of medical iatrogenesis has broadened in its scope beyond the clinical setting, and includes definitions of social iatrogenesis (generally understood as medicalization of life and aspects of clinical practice and medical industries that lead to excessive dependence on medical care) and cultural iatrogenesis (when medicalization leads to cultural harm due to loss of traditional ways in dealing with disease and illness).[6,7]

Drug safety issues arising from forms of iatrogenesis continue to be a problem in our modern and increasingly health-driven society. This includes a national prescription drug abuse epidemic that continues to cause significant patient safety, social, and economic harms, the causes of which can often be traced to failures in appropriate clinical diagnosis and treatment, medicines prescribing, and controlling access to prescription drugs with abuse potential.[8] Despite these recognized patient safety and public health risks, drug-related iatrogenesis may be expanding far beyond these known risk areas into new and uncharted territories. This specifically includes the emergence of new and disruptive forms of digital technologies that now allow consumers the ability to source questionable health information and access healthcare services and products outside of the traditional healthcare setting.[8,9]

Though these digital technologies, such as the rapidly expanding "Health Internet" and social media, have the potential to enable consumer choices and awareness of health issues, unregulated and uncontrolled expansion has also led to clear online patient safety harms. In fact, of the 87% of U.S. adults that use the Internet, 72% of them looked for health information online for specific diseases or conditions, treatments or procedures, and for doctors or other health care professionals, yet the quality of the various sources of online health information is questionable.[10,11] Hence, the concept of medical iatrogenesis may require modernization to include a new category of "digital iatrogenesis" that reflects the current realities of our social-media and online environment, particularly as it relates to safety of medicine's access worldwide.

The Digital Global Counterfeit Drug Trade

A relatively new phenomenon that has emerged from the evolution of the Internet and related technologies is the online pharmacy. It is important to note that the fundamental concept of an "online" pharmacy is not in itself unique, as the growth of e-commerce has included virtually all aspects of the economy and participating industries, including health. Yet, a key difference between the pharmacy

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industry and other e-commerce platforms (e.g., consumer goods, travel sites, software, etc.) is that they function with the purpose of distributing regulated pharmaceuticals directly to consumers, a practice that requires authenticity/assurance of the product quality, licensure of the establishment, as well as appropriate dispensing authorized and overseen by a health professional (i.e., physician, pharmacist, etc.).[12]

Despite well-established legal and regulatory requirements needed to operate traditional brick and mortar pharmacies in virtually all jurisdictions, few countries have specifically regulated the online pharmacy industry.

[13]Exacerbating the lack of targeted regulation are findings that the majority of online pharmacies do not adhere to existing pharmacy laws and regulations even when they apply in jurisdictions where they purport to operate.[14] Indeed, illicit or "rogue" online pharmacies that operate in clear violation of applicable laws, are now a well-recognized public health and patient safety threat, and have been associated with patient injury, death, drug adverse events, and importantly have digitized the international criminal trade of counterfeit/spurious/falsified/fraudulent medicines.[9,12,15] The international community is starting to take notice, with the World Health Organization, Interpol, the UN Office of Drugs and Crime, the US Food and Drug Administration (FDA), the National Association of Boards of Pharmacy (NABP), and other organizations now actively warning consumers about the dangers of purchasing drugs online.[9]

Many of these rogue online pharmacies share similar characteristics and marketing tactics aimed directly at the consumer that are clear causes of iatrogenic conditions. These include "no prescription" online pharmacies that do not require a prescription from a consumer for drug purchase or may use other illegal methods to justify dispensing without a prescription (e.g., use of a dubious medical questionnaire or a providing a fraudulent prescription—for a price).[12] Sites also often market versions of branded pharmaceutical products subject to patent or exclusivity protections as "generics," even though a generic formulation is neither available nor authorized. Importantly, these sites focus on key aspects of medical consumerism potentially exacerbating social iatrogenesis effects, including encouraging consumers to seek drug treatment and offering ease of access and convenience to entice consumer purchasing without appropriate oversight or understanding.[16]

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Common iatrogenic effects can also result from consumers purchasing from illicit online pharmacies even if a product is authentic. This includes patients self-diagnosing a medical condition and treating it incorrectly, negative drug interactions due to lack of clinical oversight, possible drug addiction from use of controlled substances, and lack of clinical monitoring and follow up to determine if treatment is effective.[9,12] However, arguably, the greatest risk emanates from possible consumption of fraudulent or counterfeit product that can result in direct patient harm.[12] These iatrogenesis-related risks are further amplified by the online presence of drugs that represent clear and arguably irrefutable patient safety risks.

Dangerous Drugs Online

In the presence of certain clearly dangerous drugs online, appropriate regulation of online pharmacies to ensure equitable and safe access to medicines for populations that desperately need treatment points to the need for immediate policy attention. This need is reified as recent studies have found that key drugs have been subject to suspect sales, including vaccines, narrow therapeutic index drugs ("NTIs"), drugs subject to recall/withdraw, and drugs that have not even received regulatory approval for sale being offered by online pharmacies.

For example, in the case of vaccines, a study in the journal Vaccine in 2012 found that all vaccines listed on FDA Biological Shortage list (including Hepatitis A&B vaccines, and Zoster vaccine) were available online.[17] The search was then expanded to assessment of online availability of all vaccines listed on the WHO Essential Medicines List (EML), where a similar result was found with all EML vaccines observed as available from online pharmacies.[17] Online availability of vaccines introduces some clear patient safety issues. To begin, even if product is authentic at the time of shipment, most biologics/vaccines require proper cold storage for shipment in order to ensure potency, a practice that may or not be practiced by online sellers. Further, once a product is delivered to an end-user consumer, that individual may not have the appropriate training or instructions to self-administer the vaccine, further bringing into question the viability of these products when sourcing them online. In addition, several sellers observed in the study advertised their vaccines as "over-the-counter" (a clear form of fraudulent marketing) and were international in origin or NABP "not recommended", further highlighting potentially safety risks.[17]

The NTI drug class is also an important illustration of the clear risks to patients from purchasing online. NTI drugs are those medicines that have a narrow proximity between therapeutic and toxic amounts and have been associated with higher risk of adverse events.[18] These drugs require close professional oversight when administering which is clearly absent in online drug purchasing. Further, NTI drugs require precise manufacturing of the product and often rely on originator information to establish bioequivalence, a situation which makes attempted counterfeiting an even more dangerous proposition.[18] Yet, despite NTI risks, a study in Clinical Therapeutics in 2013 found that 92% of "core" NTI drugs were available online without a prescription.[18] This is extremely concerning, as patients may reasonably attempt to obtain currently used medication forms on which they are stable, potentially leading to online purchases of questionable product.

Even more disturbing Internet developments are of concern. For example, online patient safety issues arising from online pharmacies are the purported offering for sale of drugs that have yet to receive regulatory approval for sale. Such is the case for anti-obesity drug Belviq® (Lorcaserin), which at the time of a 2013 study in the journal Obesity, had received FDA approval, but was not legally on the market as it awaited U.S. Drug Enforcement Agency scheduling as a controlled substance.[19] Despite not being legally available on the market, the study found that Belviq was not only actively being marketed, it was being also marketed for sale as a "no prescription" drug by online vendors and in large kilogram quantities by business-to-business wholesalers (B2B).[19] What exactly was being purported to be sold by these online vendors is unclear, but due to the product's unapproved status, all sales would be illegal.[19]

Finally, another class that appears to be a clear patient safety risk are drugs subject to drug regulatory agency permanent recall or withdraw. Though research is still pending, unpublished studies currently in development by authors of this piece have identified that many drugs subject to global permanent recall (including drugs associated with adverse risk of cardiovascular events

such as Mellaril (Thioridazine) and Darvocet (Dextropropoxyphene)) are actively marketed for sale online by illicit online pharmacies, via social media, and by B2B wholesalers including Alibaba.com. Permanently recalled/withdrawn drugs offer yet another example of a clear patient safety threat as these drugs are generally no longer available on the market (bringing into question their authenticity) and can introduce significant patient safety risks and direct and indirect harms.

Digital Iatrogenesis

Collectively, research and law enforcement activities relating to online pharmacies and Internet drug sales provide compelling examples of why the constantly changing and evolving digital health landscape requires the attention of the policy community in the context of iatrogenesis and broader patient safety concerns. Similar to Ivan Illich's broadening of medical/clinical iatrogenesis to include social and cultural concepts first in 1974 in his book Medical Nemesis,[20] we advocate for recognition of a new concept of "digital iatrogenesis" loosely defined as "preventable patient harm and injury that occurs from use of information, services or products delivered or enhanced through the Internet and related technologies." This definition is broad enough to recognize the potential for the iatrogenic effect emanating from illicit online pharmacies, as well as the diffusion of poor quality and misleading health information online that can result in patient harm.[11,21] Our definition also follows on prior efforts aimed at modernizing iatrogenesis to the increasingly technology and electronically driven medical world through the development of concepts of "technological iatrogenesis" and "e-iatrogenesis" (generally described as emerging errors stimulated by the infusion of technological innovations into complex healthcare systems or electronic sources of errors.)[1]

Through this process, global governance for e-Health and the Health Internet can occur. Cooperative mechanisms can then be integrated that includes a focus upon inclusiveness of all stakeholders, public and private, domestic and global, patient and provider, to join to work on the global goal of a safe digital health system.[9] In concert with efforts by international organizations such as WHO, UN Office of Drugs and Crime, and Interpol, digital iatrogenic harm can both be avoided and proactively eliminated dynamically.[22] With improvements in coordination and oversight of public health and law enforcement authorities, this system can be adaptive to address the varying needs of regions and sovereignties against avoidable harm that is the hallmark of iatrogenesis.

Conclusion

Most countries recognize Cicero's important conception: salus populi suprema lex—the health of the people is the highest law.[23] As the Internet becomes a more predominant source of health information,[24] consumers must be protected from dangerous and illicit online vendors who seek their own profit at the expense of patient safety, often with dire consequences. As our digital environment continues to expand, so does the need to expand the concept of iatrogenesis to respond to the increasingly digital health society. Policymakers, public health and medical professionals, and the law enforcement community must ensure that health is kept safe online so that we may be able to fulfill Cicero's ancient but fundamental maxim.

Acknowledgements. Tim K. Mackey received funding from the Canadian Social Sciences and Humanities Research Council in support of research regarding online access to recalled/withdrawn drugs and greatly acknowledges this support.

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