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RESEARCH ARTICLE

Illicit Internet availability of drugs subject to recall and patient safety consequences

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Abstract *Background* Permanently recalled drugs are a public health concern if they remain accessible in violation of applicable regulation. Illicit online pharmacies act as an alternative form of access and have been associated with the sale to patients of counterfeit/falsified/fraudulent/substandard drugs. We wished to determine if permanently recalled and significantly restricted drugs were illegally marketed for sale online. *Objective* The study was conducted in two phases with two objectives. The first phase attempted to identify drugs subject to permanent recall in certain major pharmaceutical markets as well as those listed as recalled or significantly restricted by the United Nations. We also examined the market authorization status of identified drugs in China and India. The second phase used structured searches on the Internet to determine if identified drugs were marketed for sale online. *Setting* The World Wide Web. *Method* After identification of permanently recalled and restricted drugs we conducted Internet searches for illegal "no prescription" marketing events. We assessed the form of marketing, whether a site offered direct-to-patient sale, use of social media marketing, and the site's compliance status with external monitoring bodies. *Main Outcome* Number of recalled drugs marketed as available for purchase on the Internet. *Results* We identified 16 class I equivalent permanently recalled or restricted drugs, 56.3 % (n = 9) of which maintained market authorization in either China or India. Half (n = 8) were marketed for sale online without a prescription direct-to-patient. Use of social media marketing was mixed, with only 18.8 % (n = 3) of recalled drugs having a presence on Facebook, though 50.0 % (n = 8) had content on Twitter. We also found the majority (68.8 %, n = 11) were available and marketed for sale by vendors on the wholesale/business-to-business website alibaba.com primarily as active pharmaceutical ingredient. *Conclusion* Despite efforts in several countries to restrict access to these drugs or permanently remove them from the market, our study indicates that various sources actively market recalled drugs for sale online. Drug regulators, public health agencies, and law enforcement officials should act with urgency to appropriately restrict and regulate these sales to protect global patients and consumers.

Keywords Drug recalls · Drug withdrawals · Internet pharmacies · Market removal · Online pharmacies · Public health · Social media marketing

Impact of Findings on Practice

- Patients, clinicians, and pharmacist should be aware that drugs subject to permanent recall or otherwise significantly restricted are actively marketed for sale on the Internet.

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- Permanently recalled or restricted drugs purchased online may be of questionable quality/authenticity and also introduce serious patient safety risks if consumed.
- Websites purporting to sell recalled or significantly restricted drugs are likely higher risk and should be avoided by the public and healthcare practitioners.

Introduction

The process of removing a drug from the market in order to reduce potential risk to human health is a critical post-marketing surveillance function of drug regulatory authorities ("DRA's") around the world. A drug recall, in which a product is either temporarily or permanently removed from the market, is often voluntarily initiated by the manufacturer or may be conducted at the request or order of a DRA [1]. It is important to note that depending on the jurisdiction, different terminology and categories of drug recalls, defects, market withdrawals, and safety alerts can result in varying situations of product removal, correction, limited access, or safety notification (See supplementary information).

The most serious type of recall generally involves situations where there is a reasonable probability that continued use will cause serious adverse health consequences or even death. In most developed countries, these events are categorized as "Class I" recalls and can result in the removal of a specific batch of products due to quality defects or permanent removal of a specific drug product due to inherent concerns about the safety and/or risk–benefit profile. Importantly, discovering serious adverse effects of drugs in the post-marketing phase is not necessarily uncommon [2]. This includes the recall of "blockbuster" drugs that have been prescribed to million of patients worldwide, subsequently being removed from the market due to serious safety concerns [3]. Yet, effectively coordinating the permanent removal of a drug to ensure the protection of global public health can be challenging, as evidenced by the 2004 global recall of Rofecoxib (Vioxx) [2, 4, 5].

Recently, a rise in overall drug recalls has made this an important global patient safety issue [6, 7]. As an example, a recent study found that 4.2 % of all drugs approved in Canada between 1990 and 2009 were required to be withdrawn due to safety concerns or negative benefit-to-harm ratio [8]. Similarly, a recent study on drug alerts issued by the UK Medicines and Healthcare Products Regulatory Agency ("MHRA") found that there was a tenfold increase in the number of defective medicine incidents reported from 2001 to 2005 [9]. Further, DRA drug recalls can lead to drug shortages and impact patient treatment access for diseases with few therapeutic options or that lack appropriate formulations [10, 11].

Despite clear safety risks associated with recalled medicines, other avenues of unregulated access outside DRA oversight may be available. This includes the marketing and sale of pharmaceuticals by illicit online pharmacies. We define illicit online pharmacies as websites that advertise "no prescription" sale of prescription drugs in violation of customary law. These websites may be involved in the sale of substandard, counterfeit, and fraudulent/falsified products that may contain incorrect or no active pharmaceutical ingredient ("API"), and/or toxic agents and have been associated with patient deaths (e.g. 2001 prescription drug overdose of U.S. teenager Ryan Haight and 2006 death of Canadian Marcia Bergeron) [5, 12–17].

Online pharmacies also utilize aggressive direct-to-consumer advertising that includes false and misleading information, sell illegitimate fraudulent "prescriptions", and use popular social media platforms to market their services [5, 12, 13, 18–21]. Studies have also found they sell a wide-variety of pharmaceutical products, including drugs subject to abuse, analegsics, antidepressants, contraceptive products, drugs subject to shortage, narrow therapeutic drugs, unapproved drugs, and vaccines, all marketed for sale without a prescription online [14, 21–31].

Aim of study

Permanent recalls can only be effective if there is sufficient DRA oversight of any ongoing restricted access and if unregulated sources are controlled. If, however, there are illicit sources (e.g. online pharmacies), a permanent removal or access restrictions may not be sufficiently effectuated. Consumer purchasing may also be impacted by inadequate consumer information on recalled drug status, as previous research has reported lack of adequate web-based information for important drug safety warnings (including drug recalls) [32]. Hence, we sought to assess if online pharmacies are actively marketing the sale of drugs subject to permanent recall or subject to access restrictions.

Ethical approval

Ethical approval was not necessary as the study did not involve human subjects related research.

Method

The study was conducted in two phases (see Fig. 1). The first phase attempted to identify drugs subject to permanent recall or restricted access in two groups: (1) select large pharmaceutical markets; and (2) those listed as banned, withdrawn, severely restricted, or not approved by 24

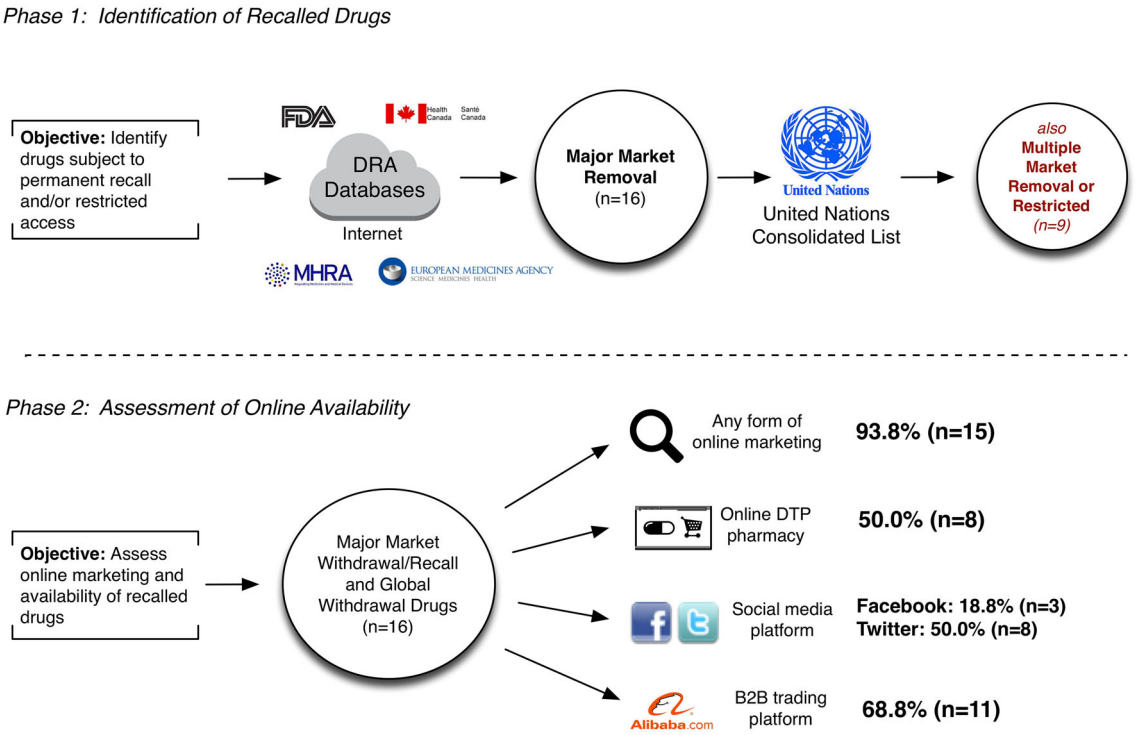

Fig. 1 Study strategy and summary of results

countries as compiled by the United Nations. To accomplish this, we conducted a document and database review of DRA information sources and the 14th Issue of the UN Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved By Governments ("UN List"). In the second phase we attempted to identify if the drugs identified in these two groups were marketed for sale online using search methods from previous published studies [14, 23, 33, 34].

Phase 1: Identification recalled drugs

We focused on drugs subject to the equivalent of a "Class I" recall that were subsequently permanently removed from the market or subject to significant access restrictions [1]. This did not include drugs that constituted a Class I recall only for a specific batch of products due to an acute quality issue. We used the Class I category as it represents the most immediate risk to individual and population-based health.

We first reviewed DRA websites for the USA, United Kingdom, European Union, and Canada and searched for Class I drug recalls and then attempted to determine if the product was permanently removed and/or had its access significantly restricted. These countries were selected due to their market size and accessibility of data sources. If the drug was subject to a Class I recall and permanent removal, or if it had never received DRA marketing approval in all four countries, it was categorized as a "Major Market Removal." We also wished to determine if a Major Market Removal drug was also cross-listed on the UN List. If a drug meet both of these criteria, it was classified as a "Multiple Market Removal or Restricted" drug. We limited drug recall events to those occurring during the 10-year period from 2002 to 2012 and also assessed the therapeutic class and reason for recall.

Finally, we also assessed the marketing authorization status of identified drugs in China and India given that these countries are major suppliers of generic drugs and API globally. The status and timing of recall, removal, or continuing market authorization in these countries is important to examine in order to assess its impact on continued manufacturing and global trade in these medicines, as well as availability of these drugs for online sales. Review was conducted from June to October 2013.

Phase 2: Examination of marketing characteristics

After we identified drugs subject to Major Market Removal or Multiple Market Removal or Restricted classification, a *Google* search was performed using the term "buy no prescription [Recalled Drug Name]" using both International Nonproprietary Name ("INN") and proprietary/

brand name to determine if drugs were actively marketed for sale online. The first five pages of search results were examined and results were divided into three different marketing categories (see Table 1 for categories and definitions). Websites that were engaged in direct-to-patient sales ("DTP") were also assessed for potential risk status by determining if they were categorized by external monitoring bodies as lacking compliance, or possibly violating applicable laws or regulations [35, 36]. The use of these external sources provides some information regarding the quality and potential risks to consumers associated with buying from these websites and are used by law enforcement, technology providers, and the industry.

In addition to conducting search engine queries, we also assessed whether identified drugs were advertised using popular social media sites Facebook and Twitter. Facebook searches were performed using the Facebook in-site search box with the default search term "all the pages named [Recalled Drug Name]" and then assessing whether a related Facebook page advertised the sale of a recalled drug. A positive result was defined as a Facebook page advertising a recalled drug in its content or providing links to an online pharmacy for purported sale. For Twitter, searches were conducted by querying "No prescription [Recalled Drug Name]" in the Twitter search box and then identifying tweets that purported the sale of the recalled drug or provided a link to an online pharmacy.

Finally, we wished to determine if business entities on the global B2B trading platform Alibaba.com were marketing the sale and/or trade of wholesale/large quantities of identified drugs. We limited our search to Alibaba.com as it is the largest B2B website globally and is a community for numerous B2B vendors. We conducted our searches in the available site-wide search box using both the INN and proprietary name of the recalled drug. We then reviewed purported B2B vendors to determine if they were advertising the sale of a finished pharmaceutical product and/or API.

All structured online searches and website content analysis were conducted from October to December 2013.

Results

Phase I: Recalled and restricted drugs

A total of 16 drugs were identified as subject to Major Market Removal [12 oral and 4 injectable formulations (Table 2)]. Nine (56.3 %) of these drugs were also identified as Multiple Market Removal or Restricted. There was a diverse set of 11 therapeutic classes identified with anti-inflammatory (n = 3, 19 %) the most commonly recalled or restricted. Recalled drugs had several indications, although many were permanently removed from the market or restricted due to the risk of cardiovascular adverse events. The majority (56.3 %, n = 9) of these drugs maintained their market authorization status either in drug or API form in either China or India. Even when market authorization was removed/prohibited, the time lapse between first year of removal in a major market and removal in India took as long as 3 years.

Phase 2: Online marketing

Of the 16 drugs we reviewed that were classified either as Major Market Removal and/or Multiple Market Removal or Restricted, all but one (93.8 %, n = 15) was marketed in some form online (Table 3). Recalled drugs were marketed by a variety of websites including affiliate sites, user forums, membership sites, and other mediums, though only half (50.0 %, n = 8) were actually advertised for sale DTP by an online pharmacy (See supplementary information for examples). Of the 8 drugs marketed DTP, all were marketed by websites categorized as either "rogue" or "unapproved" by the private Internet monitoring company LegitScript.com, an unsurprising finding given marketing

Table 1 Examination of marketing characteristics—categories and definitions

Category	Platforms	Definition
"Any Form"	Individual websites that host Internet marketing/links, user forums, marketing affiliates, or other web marketers/data aggregators	Any form of online advertisement that includes advertisements marketing the sale of recalled drugs but do not sell directly to patient. Websites include web links to separate website for purchasing
"Direct-to-Patient" (DTP)	Online pharmacy websites	Defined as at least one instance of an online pharmacy allowing consumers to select the recalled product and then add it to an online shopping cart for purchase
"Businesss-to-Business" (B2B)	Alibaba.com	E-commerce platforms that act as web portals to generally connect Chinese manufacturers with overseas buyers. Primarily offer wholesale trade of finished pharmaceutical products and active pharmaceutical ingredient

Table 2 List of major market removal and multiple market removal or restricted

INN name of drug (proprietary name)	Year of approval	Year of first removal	Indication and reason of removal		Recall status by country^				Market authorization status	
					USA	Canada	EU	UK	China	India (date prohibited)
Oral formulation drugs										
Levomethadyl acetate hydrochloride **(Orlaam)**	1993	2003	Indication	Management of opioid dependence	R	Never approved	R	R	No	No
			Reason	Life-threatening cardiac disorders						
Rofecoxib **(Vioxx)**	1999	2004	Indication	Osteoarthritis, rheumatoid arthritis, acute pain, dysmenorrhea, migraine	Multi-country removal and/or restriction (UN)				No	No (Dec 2004)
			Reason	Risk of cardiovascular events						
Pemoline **(Cylert/Volital)**	1975	2005	Indication	Attention deficit hyperactivity disorder	Multi-country removal and/or restriction (UN)				Yes[1]	No
			Reason	Life-threatening hepatic failure						
Thioridazine **(Mellaril)**	1962	2005	Indication	Schizophrenia	Multi-country removal and/or restriction (UN)				Yes[2]	No[4]
			Reason	Cardiac arrhythmias and sudden death						
Valdecoxib **(Bextra, Valdyn)**	2001	2005	Indication	Osteoarthritis, rheumatoid arthritis, dysmenorrhea	Multi-country removal and/or restriction (UN)				No	No (July 2005)
			Reason	Unfavorable benefit-risk profile						
Ximelagatran **(Exanta)***	2003	2006	Indication	Anticoagulant	Multi-country removal and/or restriction (UN)				No	No
			Reason	Serious liver injury						
Lumiracoxib **(Prexige)**[#]	2006	2007	Indication	Osteoarthritis, pain associated with primary dysmenorrhea, dental surgery and orthopedic surgery	Multi-country removal and/or restriction[a] (UN)				No	Yes
			Reason	Risk of serious side effects affecting liver						
Tegaserod Maelate **(Zelnorm)**	2002	2007	Indication	Irritable bowel syndrome	Multi-country removal and/or restriction (UN)				Yes[3]	No (Mar 2011)
			Reason	Potential for heart attack, stroke or worsening of chest pain that can turn into a heart attack						
Rimonabant **(Acomplia)**[#]	2006	2009	Indication	Management of obesity	Multi-country removal and/or restriction[a] (UN)				No	No (Dec 2009)
			Reason	Risk of psychological side effects						
Dextropropoxyphene and Propoxyphene Napsylate **(Darvocet, Darvon)**	1972	2010	Indication	Relief of mild to moderate pain	R	R	R	R	Yes[1]	No (May 2013)
			Reason	Risk of potentially serious or fatal heart rhythm abnormalities						
Sibutramine hydrochloride **(Meridia, Reductil)**	1997	2010	Indication	Management of obesity	R	R	R	R	Yes[3]	No (Feb 2011)
			Reason	Increased risk of heart attack and stroke						
Sitaxentan **(Thelin)**	2006	2010	Indication	Pulmonary arterial hypertension	Never approved	R	R	R	No	No
			Reason	Hepatotoxicity						

Table 2 continued

INN name of drug (proprietary name)	Year of approval	Year of first removal	Indication and reason of removal		Recall status by country^				Market authorization status	
					USA	Canada	EU	UK	China	India (date prohibited)
Injectable drugs										
Aprotinin **(Trasylol)**	1993	2007	Indication	Prophylactic used to reduce perioperative blood loss	Multi-country removal and/or restriction[b] (UN)				Yes[1]	No
			Reason	Increased risk of death						
Efalizumab **(Raptiva)**	2003	2009	Indication	Chronic moderate to severe plaque psoriasis	R	R	R	N/A	No	No
			Reason	Risk of developing progressive multifocal leukoencephalopathy (PML)						
Gemtuzumab Ozogamicin **(Mylotarg)**	2000	2010	Indication	Acute myeloid leukemia	R	N/A	Never approved	Only for experimental use	No	Yes
			Reason	Unfavorable benefit-risk profile						
Drotrecogin Alpha **(Xigris)**	2001	2011	Indication	To decrease mortality in patients with sepsis	R	R	R	R	No	Yes
			Reason	Unfavorable benefit-risk profile						

Data sources for recall/removal status in USA, Canada, EU, and UK: US FDA Recall, Market Withdrawals and Safety Alerts website, FDA Enforcement Reports, Health Canada Recalls and Safety Alerts Database, UK MHRA Drug Safety Update newsletters, and European Medicines Agency European Public Assessment Reports of Withdrawn medications. For market authorization status in China and India: SFDA Domestic, Imported, and approved Active Pharmaceutical Ingredients (APIs) and API manufacturers in China database, and India Central Drugs Standard Control Organization (CDSCO) List of Drugs Prohibited for Manufacture and Sale Through Gazette Notifications under Section 26A of Drugs and Cosmetics Act 1940 by the Ministry of Health and Family Welfare and CDSCO Updated List of FDC and New Drugs Approved for Marketing in India 1971–2014

R, Class I recall with either permanent removal (market withdrawn)

* First approved in France

First approved in European Union

^ The term "multi-country removal and/or restriction" indicates that the drug was (1) removed or restricted in the USA, Canada, EU, and the UK per notes; and (2) listed on the UN List. However, some recalled or restricted drugs may not be listed on the UN List as the data in this list has only been updated to 2008. Hence, some drugs post-2008 data may also be removed or restricted in multiple countries/markets

[1] Listed in both SFDA domestic drug database and list of approved API and API manufacturers database

[2] Listed in SFDA domestic drug database but not listed as approved API

[3] Not listed in SFDA drug database but listed in approved API and API manufacturers database

[4] Not listed in India CDSCO drug approval status lists from 1971 to 2014 and not listed in CDSCO prohibited list

[a] Never approved in United States

[b] EMA scientific committee recommended suspension be lifted and Nordic Group acquired marketing authorization rights from Bayer HealthCare (July 2012)

Table 3 Online marketing of recalled drug

INN name of drug (proprietary name)	Any form of marketing (Y/N)	Website selling direct to patient (Y/N)	Website status^		Social media		B2B	
			NABP not recommended	Status on LegitScript	Facebook	Twitter	API	Finished product
Oral formulation drugs								
Levomethadyl acetate hydrochloride **(Orlaam)**	**Yes**	No	N/A	N/A	No	No	No	No
Rofecoxib **(Vioxx)**	**Yes**	No	N/A	N/A	No	**Yes**	**Yes**	**Yes**[1]
Pemoline **(Cylert/Volital)**	**Yes**	No	N/A	N/A	No	**Yes**	No	No
Thioridazine **(Mellaril)**	**Yes**	**Yes**	Not listed	Rogue	No	**Yes**	**Yes**	No
Valdecoxib **(Bextra, Valdyn)**	**Yes**	**Yes**	Not recommended	Rogue	No	**Yes**	**Yes**	No
Ximelagatran **(Exanta)***	No	No	N/A	N/A	No	No	No	No
Lumiracoxib **(Prexige)**[#]	**Yes**	**Yes**	Not recommended	Unapproved	No	No	**Yes**	No
Tegaserod maelate **(Zelnorm)**	**Yes**	**Yes**	Not recommended	Rogue	No	**Yes**	**Yes**	No
Rimonabant **(Acomplia)**[#]	**Yes**	**Yes**	Not listed	Rogue	**Yes**	**Yes**	**Yes**	No
Dextropropoxyphene and propoxyphene hydrochloride **(Darvocet, Darvon)**	**Yes**	**Yes**	Not recommended	Rogue	**Yes**	**Yes**	No	No
Sibutramine hydrochloride **(Meridia, Reductil)**	**Yes**	**Yes**	Not recommended	Rogue	**Yes**	**Yes**	No	**Yes**[2]
Sitaxentan **(Thelin)**	**Yes**	No	N/A	N/A	No	No	**Yes**	No
Injectable formulation drugs								
Aprotinin **(Trasylol)**	**Yes**	No	N/A	N/A	No	No	**Yes**	**Yes**[1]
Efalizumab **(Raptiva)**	**Yes**	No	N/A	N/A	No	No	**Yes**	No
Gemtuzumab ozogamicin **(Mylotarg)**	**Yes**	**Yes**	Not recommended	Unapproved	No	No	**Yes**	No
Drotrecogin alpha **(Xigris)**	**Yes**	No	N/A	N/A	No	No	No	No

^ Website status categories: NABP: "not recommended" is defined as those websites that appear to be out of compliance with state and federal laws or NABP patient safety or pharmacy practices; "not listed" are websites not listed or reviewed by NABP (i.e. status unknown). LegitScript: "rogue" is categorized as a website that appears to be intentionally or knowingly violating applicable laws or regulations; "unapproved" is categorized as verified as lacking compliance with LegitScript standards or other applicable laws and regulations

* First approved in France

[#] First approved in European Union

[1] Seller(s) located in China (Mainland)

[2] Sellers located in Albania, Colombia, Denmark, the Netherlands

the sale of recalled drugs is likely in violation of applicable law in one or more countries.

Results for social media marketing of identified drugs were mixed. Only three recalled drugs (18.8 %) had a Facebook presence, though Twitter presence was much greater, with half (n = 8) marketed using Twitter. Wholesale and trading availability through B2B site Alibaba.com was more prominent with the majority (68.8 %, n = 11) of recalled drugs available either in bulk API kilogram quantities and also three products in finished form. Availability of API was predominantly from Chinese suppliers, though suppliers in Canada, the USA and Europe that appeared to be associated with research-grade API were also detected. Given the availability of "medicine grade" advertised API through B2B vendors, it is possible that this source of access and distribution could be utilized for human consumption, and not solely for legitimate uses such as research and use in non-pharmaceutical products, if not appropriately monitored and regulated.

Discussion

This is the first study to our knowledge to examine online marketing of permanently recalled or significantly restricted drugs. We found several findings that have implications

for global drug safety governance. First, although all recalled drugs identified were Class I, meaning they could potentially cause serious health problems or even death, there was no up-to-date global information source to facilitate communication of this crucial yet basic public health information. In the first phase of our study, we found limited, unorganized, outdated, and generally poorly coordination resources needed to establish a single information source describing what drugs had been permanently recalled, removed, or significantly restricted in multiple markets due to serious safety concerns.

As early as 1981, the international community through the United Nations General Assembly and the Economic and Social Council, agreed about the importance of engaging in transnational cooperation to identify and communicate information on dangerous health products withdrawn, banned, or restricted, ultimately resulting in the UN List. Yet, some 30 years later, the 14th edition only contains information updated to 2008, is not prominent in online search results (when searching for "global recalled drugs" on *Google*, it did not appear in first five pages of results), and is not provided in a convenient format. Further, the UN List has limitations that include inconsistent reporting of drug safety information from different jurisdictions with drugs banned in one country not regulated or specifically banned in another [37].

These limitations may also reflect lack of harmonization in international drug approval/removal processes, post-market surveillance approaches, and DRA communication about safety decisions as reflected in our findings that China and India continue to maintain market authorization for some of these recalled drugs. A likely factor for this lack of coordination is likely attributable to studies that have found DRAs often make different regulatory decisions based upon the same data and may also deal with uncertainty of drug evaluation in fundamentally different ways (i.e. EMA decision for full withdrawal of rosiglitazone from market compared to continued restricted access authorized by the US Food and Drug Administration) [38, 39]. Additionally, despite the high occurrence of drug recalls (approximately one per month in the USA), recent work has found that these events are not well publicized by DRAs such as the FDA [40]. Importantly, this lack of basic information on the status of recalled drugs could confuse and hamper DRA and law enforcement efforts against unregulated access points, such as illicit online pharmacies [14, 23, 34].

It should also be emphasized that in contrast to other medicines made available online that may have authorized registration/marketing status, the nature of the recalled, restricted or permanently removed drugs identified in this study present an inherent heightened patient safety risk. Beyond concerns regarding unregulated accessibility, no DTP website we observed provided information about associated risks of the recalled or restricted drug or its regulatory status. The sites also did not restrict sales to particular countries where the drug was subject to permanent recall, allowing a consumer from any jurisdiction to potentially purchase the drug. Additionally, though not all the recalled drugs identified were available directly from online pharmacies, other avenues for their sourcing may exist. Specifically, B2B vendors have the potential to sell large quantities of recalled, removed or restricted drugs (primarily in API form) to a host of global audiences (e.g. criminal elements, illicit online pharmacies, as well as individual consumers if in finished form) given that market authorization status for certain identified drugs remained approved.

Further, most drugs that have been subject to a permanent recall are no longer manufactured by the originator due to lack of marketability. This brings into serious question the quality, authenticity, and appropriateness of human consumption for recalled drugs made available online, which may not be subject to necessary DRA oversight nor current good manufacturing practices. Though we were unable to make direct purchases of identified drugs due to legal restrictions (see "Limitations" section), we note that even if the product is authentic, it may nevertheless pose inherent safety risks. If the marketed product is not the actual recalled drug advertised, it also poses risks and could lead to unanticipated drug-to-drug interactions or other complications. Hence, patients are left with an unsupervised pathway to a clearly dangerous form of online drug access with little or no information about risks, questionable drug quality/authenticity, and lack of partnership with a healthcare provider regarding use, oversight, and clinical monitoring should an adverse event be experienced.

Limitations

We had difficulty in confirming whether a drug had been subject to widespread international permanent recall when reviewing DRA sources and the UN List. This was likely due to lack of harmonization of information across different jurisdictions/reporting sources and outdated information. Specifically, information regarding drug recalls lacked consistency, making generalizations about global status of permanent recall, market removal, or restriction difficult. For example, Aprotinin (Trasylol) and Tegaserod Maelate (Zelnorm) remained available through limited access programs in the USA and Singapore, while subsequently Canada temporarily lifted marketing authorization suspension on Aprotinin in 2011; yet the EMA was also considering restricted use of the drug at the time. Additionally, China and India, who are major suppliers of API and generic versions of drugs worldwide, continued to maintain market authorization for some of the drugs examined, adding further complexity to issues regarding

ongoing accessibility. Further, online search queries for marketing and availability of drugs has certain inherent limitations. Primarily, searches in this study were conducted at a prescribed point of time, with assessment of online availability similarly limited to the study period described. However, websites are created, change, and are taken down dynamically on the Internet, hence limiting the generalizability of our results [17]. Finally, we did not determine if the marketed products were actually the advertised recalled drugs through test purchasing or quality assessment, as buying prescription drugs for a fictional patient and making payment to an illicit online pharmacy raises serious ethical and legal challenges where the study was conducted.

Conclusion

Permanently recalled, removed and restricted drugs are inherently dangerous to public health and individual patient safety. Yet our study found that they are actively marketed for sale online by an ever-expanding illicit online drug e-commerce ecosystem that includes web marketers, B2B platforms, social media advertising, and the online pharmacy itself. As these drugs present clear and immediate safety risks, regulatory, public health, and law enforcement efforts should be equally swift in ensuring that the regulatory and market authorization status of these drugs is clearly established, communicated and appropriately regulated in order to safeguard global patient safety.

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